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SURGERY

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SURGERY

VOL. 31 JUNE, 1952 NO. 6

Original Communications

ARTERIAL HOMOGRAFTS

IV. PRESERVATION OF TISSUE CULTURE VIABILITY OF CANINE AORTIC SEGMENTS AFTER FREEZING AT LOW TEMPERATURES

HENRY SWAN, M.D., JOHN J. FEEHAN, M.D., LLOYD FLORIO, M.D., AND ROY T. JOHNSON, B.A., DENVER, COLO.

(From the Halsted Laboratory of Experimental Surgery and the Departments of Surgery and Preventive Medicine, University of Colorado School of Medicine)

THE value of using homografts of blood vessels in modern surgery has been definitely established.[1-8] With present knowledge it is possible to store aorta homografts for a period of 30 days in plasma and Ringer's solution at 4° C. and still have them viable on tissue culture.[9] It is possible to use these grafts after an additional 30 to 60 days and have them function satisfactorily as conduits of blood.[10] Because human donor aortas must be obtained within six hours after death from individuals between the ages of six and thirty years who, previously in good health, were killed accidentally, it is difficult to obtain grafts for clinical use and several months may elapse before a satisfactory donor vessel is available. There is, therefore, great need for a method of preserving blood vessel homografts over an extended period of time if this technique for grafting major vessels of the body is to be practical. For the past two years, therefore, we have been investigating, by tissue culture technique, the possibility of preserving arterial segments by freezing and storing at low temperatures, utilizing methods which are as simple and inexpensive as possible and which require the minimum of special equipment.

The successful preservation of tissues by freezing at low temperatures is not new. Most of the work in this field, however, has been limited to bacteria, malignant tumor growths, and embryonic tissues. As far as can be ascertained from the literature, the preservation of adult normal tissue by freezing has met little success. This has been specifically true of arterial segments.[2, 4, 9]

Much of the pioneer work in tissue freezing was done in the field of bacteriology. Stillman[11] showed that the pneumococcus could be preserved for an indefinite period of time by freezing and drying; the gonococcus was preserved by Deakin[12] and the malarial parasites by Manwell.[13] *Treponema pallidum* has

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been shown by numerous investigators to survive extremely low temperatures and regain its motility on thawing.[8, 14] Spermatozoa, both human and animal, have been frozen rapidly at low temperatures and have exhibited motility on thawing.[15-18] The temperatures used in these experiments ranged from –196° C., the temperature of liquid nitrogen, to –269° C., the temperature of liquid helium. There were no reports as to the ability of these cells to fertilize after having been frozen and thawed.

Numerous investigators[19-24] have reported the successful freezing and storing of malignant tumor tissues of experimental animals. These tumors have resumed growth after thawing when transplanted into another experimental animal. The tumors were frozen at temperatures ranging from –74° C. to –196° C. They were stored at –74° C. for as long as 396 days.

Klinke[25] reported successful freezing of embryonic tissues with growth on tissue culture after thawing. Among the tissues treated in this manner were embryonic heart, liver, ovaries, testes, and rabbit kidney. These were frozen in liquid nitrogen at –196° C. and in liquid hydrogen at –253° C.

Among normal adult tissues, efforts have been made to establish corneal transplant banks by preserving the tissues by freezing. To date the experimental work with this tissue has met with failure.[26-28] The corneal transplants remained clear until about 10 to 14 days after transplantation when they uniformly became fibrosed and cloudy.

The problems encountered in the freezing of tissues are manifold. Among these are the temperature most suitable for freezing, the rate of freezing, the temperature of storage, the size of the tissue mass, the type of container used for holding the tissue, the media containing the tissue, and the rate of thawing. Reports in the literature show a wide variation of opinion concerning each of these.

TEMPERATURE, RATE OF FREEZING, AND TEMPERATURE OF STORING

The object of rapid freezing of tissues is to maintain the protoplasm and tissue fluids in a vitreous state without crystal formation with resultant intracellular expansion and disintegration of cell strucutre. The critical temperature range is usually given as between 0° C. and –30° C. Since the eutectic point of a calcium chloride solution is –54.9° C.[29] and the eutectic point of a combination of salts such as is found in tissue fluids would be even lower, most investigators believe that the storage of tissues must be done at temperatures below –60° C. Storage of blood vessels at –30° C. has failed to preserve growth.[2]

Although Klinke[25] obtained good results after rapid freezing by immersing the tissue directly in liquid nitrogen and liquid hydrogen, and Parker[17] showed human spermatozoa to be viable after freezing rapidly at –196° C., many observers believe that slower freezing gives a higher percentage of good results. Chang and Walton[15] introduced the term "tissue shock" after working with ram spermatozoa. They recommended a five-hour cooling time to lower the temperature to 1° C. It was found that if the temperature was lowered more rapidly all of the cells died. Breedis[19, 20] and Burmeister and associates[22] recommend cooling the tissue to 0° C. and then placing the tube containing the tissue in alcohol, adding small pieces of solid carbon dioxide so as to lower the temperature slowly about one degree per minute to –20° C. Solidification of tissue

fluids occurred between –9° C and –15° C. Breedis[20] found that with fowl trachea frozen by this method, the cilia of the epithelium were active after a period of 327 days of storage at –74° C. Olson's[22] fowl tumor frozen by this method and stored for 10 to 396 days between –64° C. and –75° C. could be transplanted without loss of potency.

It is apparent that significant disagreement exists regarding the optimal rate at which tissues should be frozen.

SIZE AND SHAPE OF THE TISSUE MASS

The size of the tissue mass is of considerable importance. The results are equally poor if the mass is too small or too large. Human spermatozoa frozen in capillary tubes with a diameter of 0.15 mm. were not motile on thawing regardless of the temperature and rate of freezing. Those frozen in capillary tubes of 0.5 mm. in diameter exhibited some motility, while those frozen in a test tube 1 mm. in diameter had abundant spermatozoa revived on thawing.[17] Suspensions of tumor cells in Ringer's or Tyrode's solution have uniformly exhibited lower survival rates after freezing and thawing than have tumors frozen in mass.

Simpson[31] froze 1 cm. cubes of tissue at –196° C. Microscopic sections of these tissues showed three definite zones of tissue reaction to freezing. A narrow outer zone (A) showed moderate disintegration of cell structure; a middle layer (B) exhibited minimal change in the cells; while the inner zone (C), which was the last to freeze, showed extensive destruction of the cells. It was our hope that blood vessels, because of their hollow lumen and relatively thin walls, would possess an ideal tissue mass for freezing with maximum zone B and minimal zones A and C.

THE MEDIA FOR FREEZING

Little attention has been directed to the media containing the tissue. Much of the freezing of tissue has been done by immersing the tissue directly in liquid nitrogen, liquid hydrogen, or other freezing agents. There are objections to this method since the gas bubbles which form on the surface of the tissue form an uncontrolled, irregular insulating layer. To prevent this, isopentane, a low boiling (30° C.) paraffin compound which freezes at –195° C. has been used as a cold transmission medium without bubble formation.[19-23] This substance, however, is mildly toxic to tissue. Snell[24] found that tissue immersed in this substance for a period of 30 minutes showed little if any damage; after one hour there was evidence of toxicity; and after 24 hours it was lethal to the tissue.

Hufnagel[5] has recently reported his experience with the freezing of blood vessels directly in liquid nitrogen. If the vessels were allowed to reach rapid equilibrium at a temperature of –196° C., a high percentage of the specimens split or cracked on nearing the equilibrium point. With the use of isopentane this complication is not encountered.

Most investigators have used saline, Tyrode's solution, and Ringer's solution as media for freezing tissues. Luyet and Hodapp[16] have shown that frog spermatozoa frozen in a suspension of 10 per cent glucose exhibited higher

survival after freezing in liquid nitrogen at –196° C. than after freezing in Tyrode's solution. This was thought to be due to the decrease in the intracellular fluid of the spermatozoa by the plasmolytic action of the hypertonic glucose solution. In working with plant tissues, these investigators had found that there was a definite relationship between the fluid content of the tissue and the ability to maintain that tissue in the vitreous state a low temperatures. They were able to freeze successfully a piece of tissue 0.1 mm. in thickness which had a 90 per cent fluid content. If the tissue fluid content were lowered to 50 per cent, it was possible to freeze a piece of tissue 0.2 mm. in thickness. Florio,[30] in working with the freezing of erythrocytes, found that a suspension of 10 per cent glucose diminished considerably the amount of hemolysis of the erythrocytes on freezing and thawing.

The ideal media in which to freeze and store tissues has not yet been established.

THE RATE OF THAWING

It is generally agreed that the thawing of tissue should be as rapid as possible to prevent the formation of ice crystals, with resultant cell destruction during the transition to the fluid state. The thawing of embryonic tissues in icy Tyrode's solution has resulted in no growth on tissue culture.[25] However, excellent growth resulted if the tissues were thawed in Tyrode's solution at room temperature. In our preliminary work, blood vessels were frozen at –196° C. Some were thawed slowly by leaving them at –10° C. for 15 minutes, at –4° C. for 15 minutes, and then at room temperature. Others were thawed rapidly by agitating in Ringer's solution heated to 37° C. Microscopic sections of the blood vessels thawed slowly revealed small clefts between the elastic fibers of the media presumed to be the result of ice crystal formation. These defects were not demonstrable in the vessels thawed rapidly. Here again the critical temperature range is thought to be between 30° C. and 0° C.

Rapid thawing appears to be essential in the preservation of tissue integrity after freezing.

THE FREEZING OF BLOOD VESSELS

Blakemore and Lord[1] were the first of modern investigators to preserve blood vessels by freezing. In their work, veins were frozen in helium in hermetically sealed tubes at –72° C. (dry ice and alcohol). These vessels were successfully transplanted after a period of storage of three months. The temperature of storage in this work is not given, and no tissue culture studies were reported.

Attempts were made by Gross and his co-workers[4] to increase the period of tissue viability over simple cold storage by freezing arterial segments. The vessels were removed immediately after the death of the animal, sectioned into the desired lengths, placed dry in hermetically sealed tubes, and immersed in a mixture of dry ice and alcohol which had a temperature of –74° C. Of thirty-two vessels frozen by this method, only two were viable on tissue culture after thawing. Transplantation of such grafts in recipient animals uniformly resulted in necrosis and rupture of the graft. Deterling and co-workers[2] subsequently repeated this work and reported similar lack of viability on tissue culture with vessels stored at –27° C.

Meanwhile, however, Hufnagel[3, 5] was having better success with vessels frozen rapidly at –196° C. in sealed tubes, stored at –74° C. for 90 days, and then thawed rapidly. Such vessels were uniformly successful as transplanted grafts. No studies were made, however, of their tissue culture viability.

EXPERIMENTAL METHOD

In this experimental work the arterial segments were removed immediately after the death of the donor animal. Under sterile conditions, the entire aorta, from the arch to the iliac arteries, was removed. As much of the adventitia as possible was removed by sharp dissection. Residual blood was removed from the lumen by irrigating with Ringer's solution. The aorta was then sectioned into 2 to 3 cm. lengths and placed in the Ringer's solution until actual freezing.

Two temperatures were used for freezing: –196° C., obtained with liquid nitrogen with isopentane as a transmitter, and –78° C., obtained with dry ice and 95 per cent ethyl alcohol. The apparatus for freezing at –196° C. consisted of a 2-liter Pyrex beaker placed in an enamel sponge can insulated by 1 inch of sheet wadding. Liquid nitrogen was poured into this beaker slowly until the violent boiling ceased and there was about 1 inch of solution in the bottom. A 500 c.c. beaker containing approximately 200 c.c. of isopentane was then immersed in the liquid nitrogen. Again time was allowed to reach an equilibrium as evidenced by beginning solidification of the isopentane. Test tubes containing the tissue were now immersed in the isopentane. Tissue freezing at this temperature was almost instantaneous.

Solid carbon dioxide in 95 per cent alcohol was used for two types of freezing procedures: one rapid, the other slow. With the rapid method, 95 per cent alcohol was put in a pan and several pieces of dry ice were added. After several minutes the alcohol became quite viscous. At this point the thermometer registered –78° C. The vessels froze firmly in this mixture in 1 to 2 seconds. For slow freezing the test tube containing the vessels was placed in alcohol at room temperature and dry ice was added at a rate which lowered the temperature 1° per minute. The contents of the test tube became supercooled at –16° C. to –18° C., after which solidification was sudden. The temperature of the alcohol dry ice mixture was then lowered rapidly to –78° C. by adding several large pieces of dry ice.

Segments of aorta were frozen at –196° C. by the following methods:

(1) directly in isopentane,
(2) in serum in aluminum foil to exclude the isopentane,
(3) in serum in an aluminum tube,
(4) in serum in a glass test tube,
(5) in Ringer's solution in a test tube,
(6) in Ringer's solution plus 10 per cent serum in a test tube, and
(7) in Ringer's solution plus 10 per cent serum plus 10 per cent glucose in a test tube.

Segments of aorta were frozen at –78° C. by the following methods:

(1) in serum in a test tube, rapidly,
(2) in Ringer's solution in a test tube, rapidly,

(3) in Ringer's solution plus 10 per cent dog serum in a test tube, rapidly, and

(4) in serum, in a test tube, slowly.

All of the equipment and utensils used in the freezing process were chemically clean and sterile. It has been shown repeatedly that a trace of certain elements can be lethal to the cells in tissue culture work. The presence of bacteria inhibits or destroys the growth of cells on tissue culture and is deleterious to the implanted blood vessel graft. Using aseptic technique, the segments of aorta were placed in small, thin-walled Pyrex tubes which were sealed with cork and further sealed by dipping the corked end into melted paraffin. The vessels were then frozen.

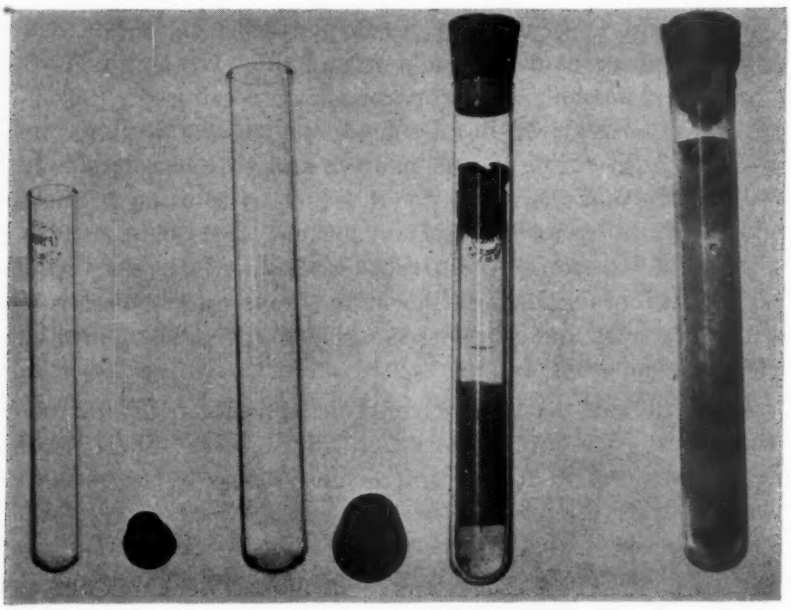


Fig. 1.—Photograph of the technique used for freezing arterial segments in nutrient media, doubly sealed in two Pyrex test tubes. The inner tube remains sterile, and is removed at time of transplantation for rapid thawing in sterile saline at 37° C.

The majority of the blood vessel segments were frozen by one of the various methods for a period of 10 to 30 minutes. They were then thawed rapidly by agitating in Ringer's solution heated to 37° C. and studied by tissue culture. This was done to ascertain which method of freezing was best tolerated by the blood vessels. It was thought that the critical period of survival would be during the freezing procedure. The vessels thus frozen and thawed were sent directly to the tissue culture laboratory in vials containing Hank's* solution with 10 per cent dog serum.

The specimens to be stored were placed in a second larger sterile test tube which in turn was corked and sealed with paraffin. These were kept either at

*Hank's Balanced Salt Solution is prepared as follows:

NaCl	.8 Gm.	$CaCl_2$	.14 Gm.
KCl	.4 Gm.	$NaHPO_4.12H_2O$	.15 Gm.
$MgSO_4.7H_2O$	.2 Gm.	KH_2PO_4	.06 Gm.

Water to 1,000 c.c.

After autoclaving add a sterile solution containing 1 Gm. glucose and 0.35 Gm. $NaHCO_3$ in 25 c.c. water.

–78° C. or at –30° C. The –78° C. storage was achieved using a large drum containing a smaller drum with about 12 inches of sawdust insulation between them. Dry ice was packed in the smaller drum and a carton in the center of the dry ice contained the test tubes with the stored vessel segments. A commercial deep-freeze unit was used for storage at –30° C.

The tissue culture technique was as follows: Eight 1 mm. squares of tissue were cut from each segment of aorta and divided between two Carrel flasks. The substrate consisted of ¼ ml. of 0.25 per cent fibrinogen. Armour's Fraction One Bovine Fibrinogen was used to make this solution. Since this material as furnished contains 50 per cent sodium citrate, 0.5 Gm. per 100 ml. water is needed to make a 0.25 per cent fibrinogen solution. The citrate does not seem to have an inhibiting effect on growth. The fibrinogen is dissolved without agitation in Hank's Balanced Salt Solution and filtered through sterile Seitz pads. The first 10 ml. of filtered fibrinogen is discarded as it will not clot (if a size 13 pad is used). The fibrinogen is spread over the bottom of the flask and clotted with one drop of thrombin (5 units per milliliter). One milliliter of the following supernatant is added as soon as the clot is firm:

2.5 parts Hank's BSS
2.0 parts dog serum
0.5 part embryo juice, 50 per cent

Phenol red, 0.005 per cent, as a pH indicator is added.

Penicillin and streptomycin, 1,000 units each, were occasionally incorporated in the supernatant fluid without any apparent deleterious effects on the growth. The flasks were incubated at 37° C., graded 1+ to 4+ indicating minimal to luxuriant growth, and discarded at the end of nine days.

FACTORS INFLUENCING TISSUE CULTURE GROWTH

Tissue culture technique itself is an intricate and delicate method of evaluating the viability of tissues, and is subject to inherent pitfalls. Causes of failure were varied and unpredictable. The most common cause was bacterial contamination which occurred despite careful aseptic technique in handling of the vessels and in spite of the use of penicillin and streptomycin in the transfer media and in the Carrel flasks. During one period, the fibrinogen failed to clot; during another, all tissues failed to grow until it was discovered that some lethal agent was apparently present in a new shipment of Seitz filter pads which were employed at that time, although these were standard filters thought to be in no way different from filters previously in use.

Because of the difficulties with the method, every group of aortic segments studied was always run with fresh unfrozen segments of the same aorta to serve as controls. Control segments uniformly showed fair to luxuriant growth after a lag period of three to five days, unless there was a failure in the tissue culture procedure itself. Accordingly, if the controls grew, the results on the specimen sent for study were accepted for analysis. If the controls failed to grow, it was interpreted as a failure of the tissue culture method. Growth of frozen segments was always one or two days slower in getting started than that of the controls. Of 592 arterial segments sent to

tissue culture laboratory for evaluation, only 341 were accepted for consideration in this analysis. The remaining 251 were discarded for reasons already discussed.

It was observed early in the study that the age of the donor animal was of paramount importance in tissue culture viability. The aorta of an animal estimated to be 12 to 14 years of age showed extremely poor growth on the control segments and no evidence of growth on any of the frozen segments. On the other hand, the aortas of puppies three weeks of age invariably showed luxuriant growth in the controls, and the frozen segments were also viable regardless of the method of freezing. Continuing experience with this aspect of the problem suggested to us that the critical age of donor animals is between one and one-half and two years (as determined by the tooth pattern). For this reason, the results of the studies on the various methods of freezing arterial segments are recorded in two groups; i.e., the over-all results and the results in animals estimated to be less than two years old.

In the early stages of the investigation, it was thought that tissue culture growth after freezing might be partially dependent upon the site of the aorta from which the segment was obtained. At first, growth in culture seemed to be poorest in segments from the arch and thoracic portions of the aorta and best from the abdominal aorta and iliac arteries. However, as our experience increased and with more careful investigation of this problem in donor animals of less than two years of age, no appreciable difference was found to exist in the viability of segments from different portions of the aorta.

On the other hand, there appeared to be individual variations in the capacity of the aorta from different animals to remain viable following freezing. Shettles[18] has previously recorded this observation in the case of human spermatozoa. This phenomenon was occasionally noted during this study when aortic segments from relatively young dogs failed to grow on tissue culture after they had been frozen by methods which had been previously yielding uniformly good results. We have no explanation for this phenomenon.

The studies attempting to evaluate the importance of different variations in the technique of the freezing process resulted in the data presented in Table I. It will be noted that several different methods resulted in a high percentage of tissue culture viability of the frozen segments.

It would appear from these data that vessels frozen in a nutrient media, that is, serum, Ringer's solution plus 10 per cent serum, or Ringer's solution plus 10 per cent serum plus 10 per cent glucose, withstood the shock of freezing better than those vessels frozen dry. One exception to this observation was the series frozen directly in isopentane at –196° C. Although 70 per cent of these vessels were viable after thawing, because of the known toxicity of isopentane to tissue after long contact, we feel that this technique offers little promise if long storage is to be employed. The method has no specific advantages and because of the inherent dangers was not fully pursued.

From the evidence obtained, it is concluded that there is no significant difference in the survival rates of aortas frozen at –196° C. as compared to those frozen at –78° C. when nutrient media are employed. At the latter temperature

TABLE I. TISSUE CULTURE RESULTS AFTER VARIOUS FREEZING TECHNIQUES

METHOD OF FREEZING	VESSELS FROM YOUNG DOGS			ALL VESSELS		
	VIABLE	NON-VIABLE	% VIABLE	VIABLE	NON-VIABLE	% VIABLE
A. At –196° C.						
1. Directly in isopentane	7	3	70.0	10	6	62.5
2. Serum in aluminum foil	–	–	–	2	4	33.3
3. Serum in aluminum tube	–	–	–	3	3	50.0
4. Serum in glass test tube	8	10	44.4	9	24	27.5
5. Ringer's solution in glass test tube	–	–	–	0	1	0.0
6. Ringer's solution plus 10% serum in test tube	10	4	71.4	11	5	68.7
7. Ringer's solution plus 10% serum plus 10% glucose in test tube	–	–	–	6	3	66.6
B. At –78° C. (rapidly)						
1. In serum in a test tube	21	7	75.0	26	35	42.6
2. In Ringer's solution in a test tube	–	–	–	0	2	0.0
3. In Ringer's solution plus 10% serum	9	4	69.2	12	13	48.0
4. Dry in a test tube	2	2	50.0	2	9	18.1
C. At –78° C. (slowly)						
1. In serum in a test tube	12	9	57.1	15	28	34.8

the results appeared to be definitely better when a rapid technique is used. Since liquid nitrogen is somewhat difficult to obtain, is extremely volatile, and difficult to preserve, it appears to us that rapid freezing with dry ice and alcohol is the more practical method of freezing aortic segments. By the use of this method in nutrient media, aortas from dogs of less than two years of age showed 70 to 75 per cent tissue culture viability.

STORAGE

We have not conducted extensive experiments to establish the length of time that tissue culture viability can be preserved by storage at low temperatures after freezing. Table II tabulates our experience to date. It is not felt that the number of experiments is sufficient to draw any significant conclusions. Two impressions, however, suggest themselves from these data. In the first place, some of the segments stored at –78° C. will be viable on tissue culture for periods up to 25 days, at least. In the second place, it would appear that –30° C. is not an adequate storage temperature to preserve culture viability. Of 18 sections stored at –78° C., seven (39 per cent) were viable, while of 10 sections stored at –30° C., none subsequently grew on culture.

TRANSPLANTATION STUDIES

The physical characteristics of the frozen graft after thawing are a little different from those of the normal vessel. The graft is contracted and slightly paler in color and has a tougher consistency than the normal vessel, all of which adds to the ease of implantation and suture of these grafts.

Seventeen of the grafts frozen by various methods were implanted into the abdominal aorta of recipient animals. All of these transplanted vessels functioned satisfactorily as conduits of blood for a period of six months. Many

TABLE II. CULTURE STUDIES AFTER STORAGE

FREEZE TECHNIQUE	DURATION OF STORAGE (DAYS)	NUMBER	NUMBER WITH GROWTH	PER CENT WITH GROWTH
	A. *Stored at 78° C.*			
1. –78° C. (rapid) in serum	12	2	0	–
	19	2	2	–
	34	2	0	–
2. –78° C. (rapid) in Ringer's solution plus 10% serum	22	5	2	–
	37	1	0	–
3. –196° C. in serum	5	2	1	–
	10	1	0	–
	19	1	1	–
	25	2	1	–
Totals		18	7	39.0
	B. *Stored at –30° C.*			
1. –78° C. (rapid) in serum	19	1	0	–
	34	2	0	–
2. –78° C. (rapid) in Ringer's solution plus 10% serum	23	6	0	–
3. –196° C. in isopentane	126	1	0	–
Totals		10	0	0.0

of the animals were sacrificed at that time for pathologic examination of the transplanted grafts. All of the transplants appeared grossly to be in excellent condition, lined with smooth glistening endothelium with elastic walls of firm consistency.

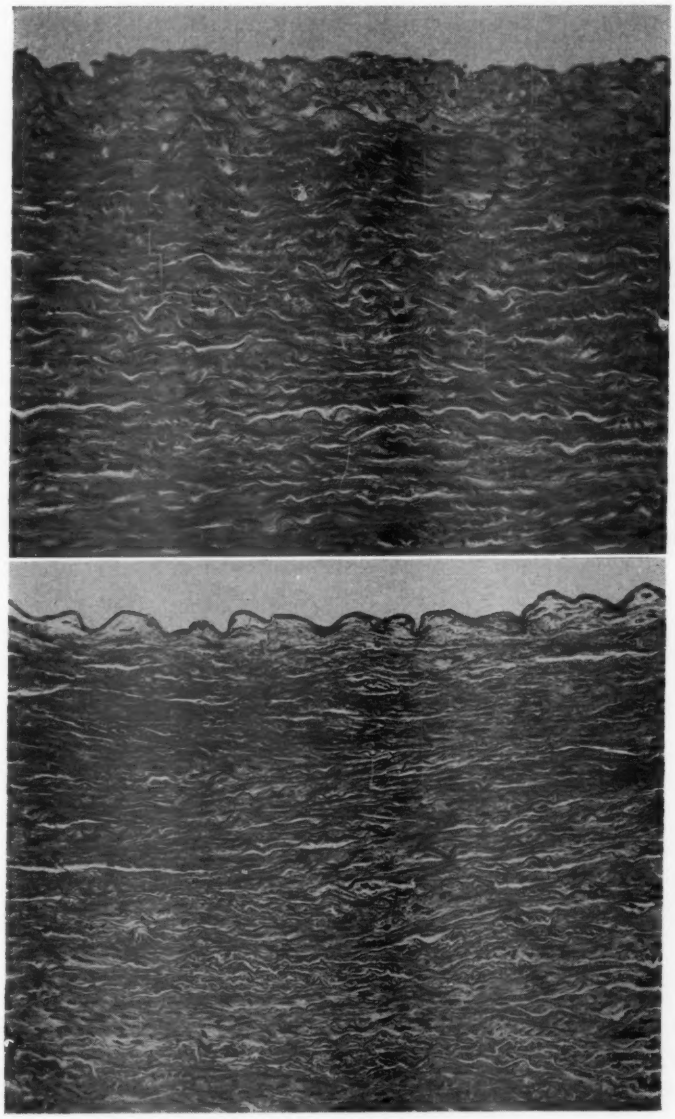
Microscopic studies were made of the grafts after freezing and storage but before implantation, as well as studies of the grafts after they had been in place in the recipient animal for six months. From these studies, the following conclusions were drawn:

In the first place, contrary to our expectation, there was no microscopic evidence that storage at –78° C. was superior to storage at –30° C. at least for periods up to five months. Before transplantation, vessels stored both ways showed remarkable preservation of tissue structure, and could scarcely be distinguished microscopically from normal aorta. When transplanted, uniform success was obtained by both methods.

On the other hand, the use of nutrient media for freezing and storage made a profound difference in the microscopic appearance when contrasted with vessels frozen dry. This is illustrated in Fig. 2. The section above (*A*) is from a vessel frozen in serum at –196° C. and stored at –30° C. for 147 days. The preservation of cellular elements seems complete, even including the endothelium. Below (*B*), the vessel was frozen rapidly at –78° C. dry, and stored at –78° C. for only three days. The epithelium has entirely disappeared, pyknotic changes in the nuclei of smooth muscle cells are apparent, and clefts have appeared in the tissue. These changes are similar to those reported by Deterling and co-workers[2] who froze their segments dry. Although both vessels functioned satisfactorily when transplanted into recipient animals, we believe the evidence is good that freezing in nutrient media results in better preservation of the cellular integrity of the artery than freezing dry.

Studies of the grafts after they had been in place in the recipient animal for 200 to 215 days revealed a microscopic picture entirely similar to that which we have previously described as occurring after the transplantation of vessels stored for short periods at 4° C.[10] The new fibrocellular intimal layer from

A.



B.

Fig. 2.—*A*, Photomicrograph of a vessel frozen at −196° C. in nutrient media and stored 147 days at −30° C. Note cellular preservation even including endothelium.

B, Photomicrograph of a vessel frozen dry at −78° C., and stored 3 days at −78° C. Note loss of endothelium, pyknotic changes in nuclei, and crystal formation.

It is felt that nutrient media are superior to the dry state for freezing of vessels.

the host was well developed, the elastic tissue of the media of the graft was intact and compressed, and the new fibrous adventitia was thinned out and largely collagenous. No significant degenerative changes were observed.

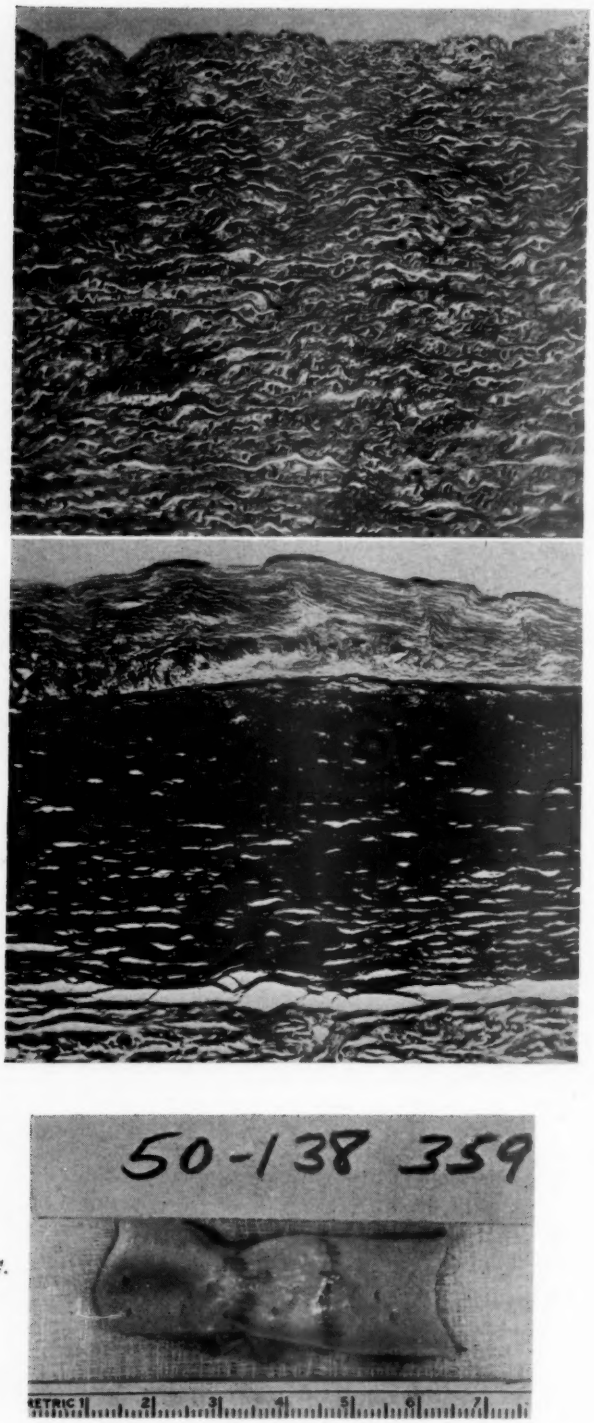


Fig. 3.—The vessel was frozen in nutrient media and stored at −78° C. for 6 days. Tissue culture showed growth. The graft functioned well and was sectioned at 206 days.

A, Photomicrograph (hematoxylin-eosin) at time of transplantation. The graft is viable *B*, Photomicrograph (elastic tissue stain) of the specimen after 206 days in recipient animal. Note fibrocellular intimal layer elaborated by the host. *C*, Gross specimen after 206 days in recipient animal.

It would appear, therefore, that at six months stored frozen grafts have resulted in a vessel which microscopically is comparable to that obtained by the transplantation of a fresh or "young" arterial graft.

DISCUSSION

This study was primarily one of applying tissue culture techniques to the evaluation of methods of freezing arterial grafts for preservation. The freezing of vessels is by no means new. Blakemore,[1] Hufnagel,[3, 5] and Deterling[2] have all previously demonstrated that frozen segments will serve satisfactorily as arterial homografts. Our few transplantation experiments confirm these findings.

We do not believe that tissue culture viability is by any means essential to successful grafting. Indeed, it is well known that formalin-fixed grafts are often successful. However, for consistency of immediate results and for the minimum of subsequent degenerative changes in arterial homografting, the optimum graft in our experience is a fresh arterial segment. These are uniformly viable on tissue culture. We feel, therefore, that a storage technique which preserves the graft in a condition which approximates the fresh state as closely as possible is desirable. Freezing in nutrient media in dry ice and alcohol and storage at the same temperature appears to accomplish this aim, and hence is the best technique currently available. Whether lyophilization will eventually prove to be superior to this method remains to be investigated.

SUMMARY AND CONCLUSIONS

1. A successful tissue culture technique for testing the viability of segments of canine aorta is described. This technique, however, is subject to technical difficulties.

2. A variety of methods for freezing arterial segments has been investigated.

3. Canine aorta can be frozen by several methods and retain tissue culture viability after rapid thawing.

4. In addition, such frozen segments can be stored at the temperature of carbon dioxide and alcohol and some, at least, will retain tissue culture viability up to 25 days of storage.

5. The age of the donor animal is an important factor in tissue culture viability after freezing. The vessels of animals under two years of age are much superior in this respect.

6. Vessels withstand freezing and storage in nutrient media much better than in the dry state.

7. The most practical and efficient method for preservation of arterial homografts at this time is rapid freezing in nutrient media in carbon dioxide and alcohol and subsequent storage at the same temperature.

8. Frozen and stored aortic grafts after transplantation give uniformly successful results which are as good as those obtained by the use of fresh aortic grafts.

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THE HEALING OF WOUNDS IN THE PRESENCE OF ANEMIA

CAPTAIN DONALD F. WATERMAN, M.D.,* AND CAPTAIN F. ROSS BIRKHILL, M.D.,**
MEDICAL CORPS, UNITED STATES ARMY, AND
CONRAD L. PIRANI, M.D.,*** CHICAGO, ILL., AND STANLEY M. LEVENSON, M.D.****
RICHMOND, VA.

(From the United States Army Medical Nutrition Laboratory, an Installation under the jurisdiction of the Surgeon General)

INTRODUCTION

THROUGHOUT most of the literature on wound healing, it is assumed that anemia per se adversely affects the healing process.[6, 10, 14] However, the few studies which have been reported on the specific effect of anemia on wound healing have not entirely supported this assumption. Most investigators have utilized an acute transient anemia and sutured incisional wounds. To our knowledge, no experimental study has been reported on the influence of anemia on the healing of open superficial defects. The present study is concerned with the effect of prolonged nutritional iron-deficiency anemia on the closure of operative full-thickness skin defects and the healing of laparotomy wounds in the albino rat.

METHODS

Albino rats (crossed Penn State and Sprague-Dawley strains) were used. Sexes were mixed, since sex per se does not influence wound healing in rats.[7] The animals were divided into three main groups in regard to diet. One group was fed cows' milk exclusively, one was fed milk liberally supplemented with iron citrate, and one was fed commercial Rockland Rat Diet.

The milk-fed rats were weaned at 26 days and placed immediately on cows' milk. Ordinary grade A, pasteurized, homogenized dairy milk was used. All unsupplemented-milk-fed animals were kept in cages which had been sprayed with aluminum paint and varnished and were given only distilled drinking water. The animals fed a supplemented milk diet and the chow-fed animals were housed in ordinary iron cages and given tap water for drinking.

Hemoglobin[1] and serum protein[11] in blood obtained from the tail vein were estimated serially.

I. *Open Wounds.*—About half the rats fed milk without iron supplementation became markedly anemic before the rest of their group. These animals and their controls were wounded earlier than the remaining animals. Accordingly,

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*Now at Blodgett Memorial Hospital, Grand Rapids, Mich.

**Now at Harper Hospital, Detroit, Mich.

***The Department of Pathology, University of Illinois College of Medicine.

****The Department of Surgery, University of Illinois College of Medicine. Now at Medical College of Virginia.

each of the three major dietary groups of animals were subdivided into two subgroups, one about 8 weeks old and the other about 19 weeks old on the basis of the time of development of anemia in the rats fed unsupplemented milk.

Under ether anesthesia, round full-thickness skin defects were made in the lower left posterior thoracic region. A biopsy punch 8 mm. in diameter was used to outline the wound which was then excised with fine scissors. Surgical asepsis was not attempted, nor were dressings used.

Degree of closure was recorded photographically, at one- to two-day intervals. The developed film was projected and traced and the area measured with a planimeter. When the wound was healed, the animal was killed and the wound area fixed in formalin. Sections stained with hematoxylin and eosin were examined microscopically.

II. *Laparotomy Wounds.*—Groups of rats were maintained on dietary intakes similar to those of the open-wound animals. The anemia of the milk-fed animals was maintained for a period of four to six weeks before operation, and throughout the postoperative period. Two groups of chow-fed animals were studied—one group as age controls, the other as weight controls. This was necessitated by the fact that the rats fed milk and iron did not gain weight as rapidly as chow-fed animals of the same age, and it appeared that weight per se had a significant influence on the healing of the incisions.

Under ether anesthesia, 3 cm. midline laparotomy incisions were made. The wounds were closed with through-and-through sutures of fine stainless steel. Surgical asepsis was not attempted nor were dressings used.

At predetermined intervals (days 3, 5, 7, 9, and 11 postoperatively) members of each group were sacrificed and the tensile strength of their wounds measured by inflating at a fairly constant rate an intra-abdominally placed condom (Kobak and associates[8]). The pressure required to break the entire wound was recorded as the tensile strength. Representative wounds were excised for histologic study as described for the open wounds.

RESULTS

By restricting the diet of albino rats to milk from the time of weaning and using aluminum-painted, varnished cages and distilled drinking water, a progressive anemia was produced, reaching a level of 5 to 7 Gm. of hemoglobin per 100 ml. of blood in from 1 to 3 months. The males became anemic somewhat more readily than the females, a fact which can apparently be correlated with their more rapid growth.

The majority of the anemic animals showed a further drop in hemoglobin concentration of from 1 to 2 Gm. per 100 ml. during the postoperative healing period, while the animals fed milk and iron maintained a practically constant hemoglobin concentration. No routine hemoglobin determinations were done in the chow-fed groups, but data from this laboratory[5] indicate that they would be expected to show levels of about 15 Gm. per 100 ml. The concentration of protein in the serum was found to be normal throughout the experiment in all groups.

I. *Open Wounds.*—The young (short-duration) anemic animals (with hemoglobin below 10 Gm. per 100 ml. for 2 weeks prior to operation) did not gain weight as fast as their iron-supplemented controls, the difference amounting on the average to 15 per cent. In turn, the animals fed milk and iron did not grow as rapidly as those on chow, the average weight of the former being about 40 per cent less. The difference between the mean weight of the older (long-duration) anemic animals (with hemoglobin below 10 Gm. per 100 ml. for 4 to 6 weeks prior to operation) and that of their iron-supplemented controls was, however, only about 8 per cent. Here again, the chow-fed animals outweighed the milk and iron group, in this instance by 25 per cent.

An initial lag period in the healing curve was not observed, although this has been described by others.[3, 4] Rather, there was contraction of the wound area within the first day, after which there was a brief (1 to 2 day) lag. Following this, wound closure proceeded rapidly until day 9, after which time the rate slowed progressively until complete healing was reached at 11.4 to 15.3 days on the average in the different groups. Contraction appeared to play a greater role in the closure of the wounds than did epithelization.

The healing curves were very similar in all groups (Figs. 1 and 2). Among the milk-fed groups, only the difference on day 9 between the long-duration anemic animals and their iron-supplemented controls proves to be mathematically significant (Fisher "t" test). This difference, however, is of questionable biologic significance in view of the fact that all other differences along the curves are not significant statistically.

In ten animals which had been anemic for 2 weeks prior to operation and whose mean hemoglobin at the time of wounding was 7.1 Gm., the average time required for wound closure was 13.2 ± 1.4 days. Their 10 milk-and-iron controls, with a mean hemoglobin at wounding of 14.7 Gm., required an almost identical time of 13.4 ± 1.9 days for complete healing. Nine similar animals fed on chow healed in 11.4 ± 1.7 days. The difference in the total healing time between each of the milk-fed groups and that of the chow-fed group is of probable significance ($p = 0.02$).

Nine animals which had been anemic for 4 to 6 weeks prior to operation and whose mean hemoglobin at operation was 5.6 Gm. healed in an average period of 14.8 ± 1.5 days, while their 14 milk-and-iron controls (mean hemoglobin at operation 14.1 Gm.) required an average of 14.7 ± 2.3 days. Eight chow-fed animals of the same age healed in 15.3 ± 2.0 days. There were no statistically significant differences among these groups.

The difference between the total healing time of the short-term and that of the long-term anemic animals is of probable significance ($p = 0.02$). This difference may be due to the difference in the ages in the two groups, since it has been shown that younger animals tend to heal faster than older animals. The difference noted between the two milk-and-iron groups is not significant ($p = 0.2$). The difference between the two chow-fed groups is highly significant ($p = 0.001$), probably illustrating the "pure" effect of age on healing, not complicated by any dietary deficiency.

Histologic study, limited to the examination of sections stained with hematoxylin-eosin, revealed no significant differences between the healed wounds of the anemic animals and those of their controls.

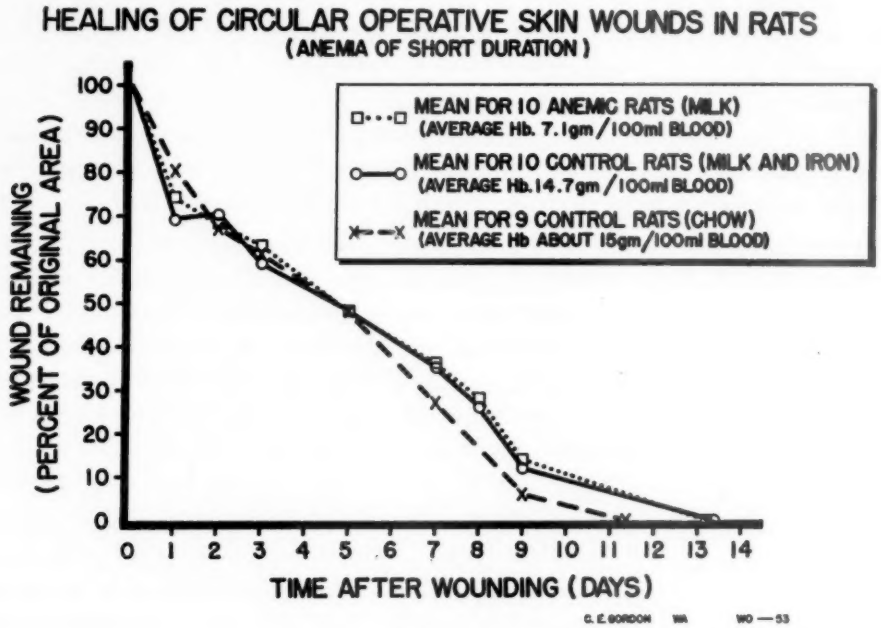
HEALING OF CIRCULAR OPERATIVE SKIN WOUNDS IN RATS
(ANEMIA OF SHORT DURATION)
WOUND REMAINING (PERCENT OF ORIGINAL AREA)
TIME AFTER WOUNDING (DAYS)
MEAN FOR 10 ANEMIC RATS (MILK) (AVERAGE Hb. 7.1gm/100ml BLOOD)
MEAN FOR 10 CONTROL RATS (MILK AND IRON) (AVERAGE Hb. 14.7gm/100ml BLOOD)
MEAN FOR 9 CONTROL RATS (CHOW) (AVERAGE Hb ABOUT 15gm/100ml BLOOD)
C. E. GORDON WA WO — 53

Fig. 1.

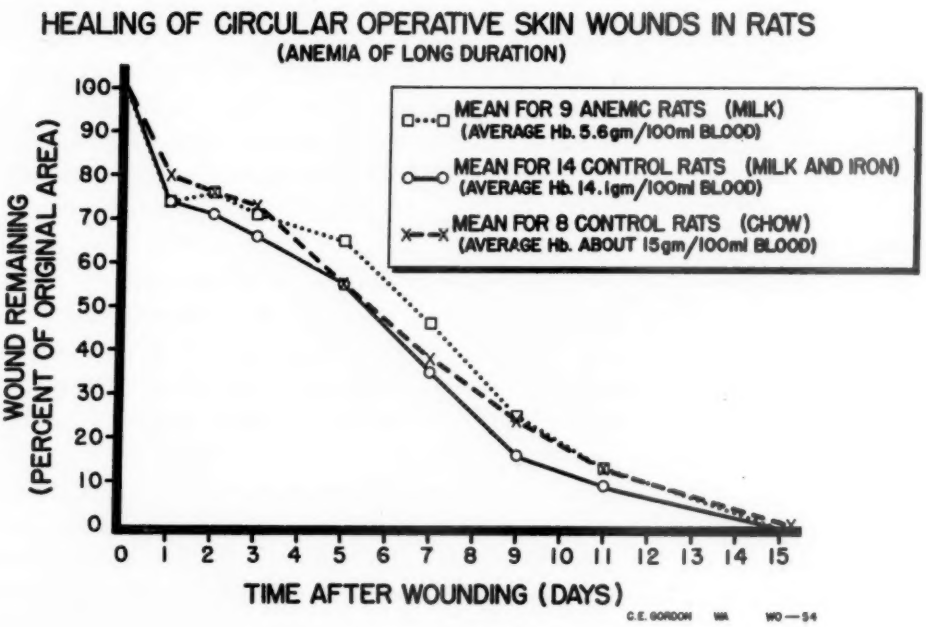
HEALING OF CIRCULAR OPERATIVE SKIN WOUNDS IN RATS
(ANEMIA OF LONG DURATION)
WOUND REMAINING (PERCENT OF ORIGINAL AREA)
TIME AFTER WOUNDING (DAYS)
MEAN FOR 9 ANEMIC RATS (MILK) (AVERAGE Hb. 5.6gm/100ml BLOOD)
MEAN FOR 14 CONTROL RATS (MILK AND IRON) (AVERAGE Hb. 14.1gm/100ml BLOOD)
MEAN FOR 8 CONTROL RATS (CHOW) (AVERAGE Hb. ABOUT 15gm/100ml BLOOD)
C. E. GORDON WA WO — 54

Fig. 2.

II. *Laparotomy Wounds.*—As was the case in the open wound series, the rats on milk or milk-plus-iron diets did not gain weight as rapidly as rats of similar age on the chow diet. Thus, at operation, the mean weight of the

anemic rats was 132 Gm., that of the nonanemic, milk-plus-iron rats, 143 Gm. and that of the chow-fed rats of similar age, 279 Gm. To control this marked discrepancy in weight, an additional group of chow-fed normal animals whose mean weight at time of operation was 146 Gm. was also studied. These rats were, of course, younger than those in the other three groups—the milk rats were about 13 weeks of age, while the weight controls were 8 to 10 weeks of age. The anemic animals had hemoglobin concentrations of 4 to 5 Gm. per 100 ml. of blood during the healing period.

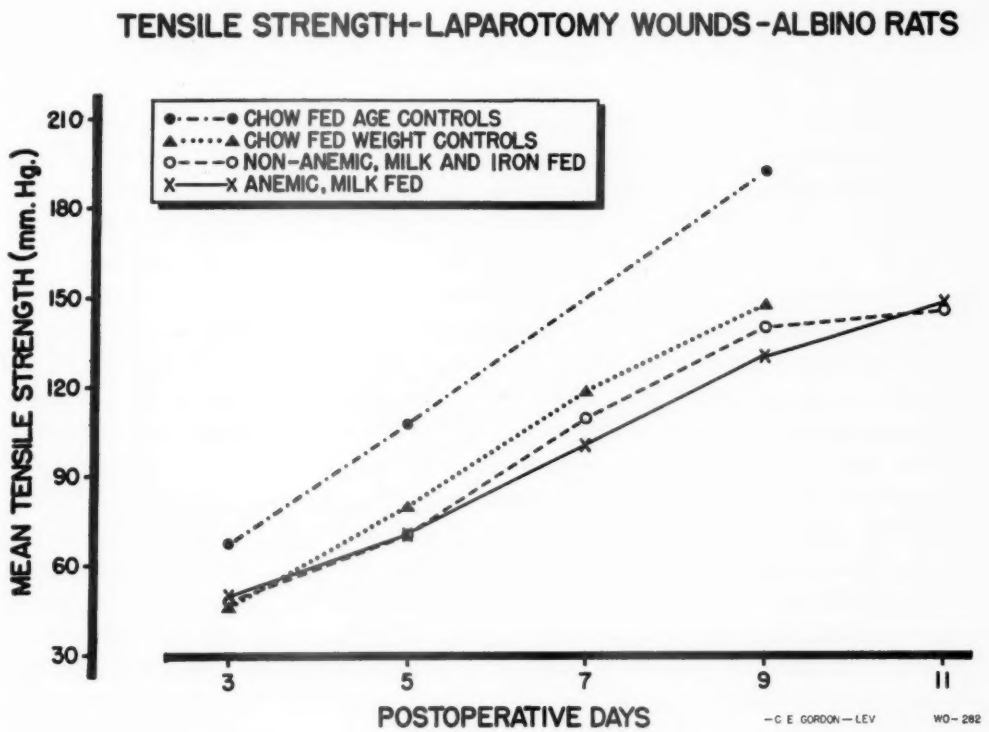

Fig. 3.—Healing of laparotomy incisions in albino rats.

The results are presented in Fig. 3. It is apparent that the curves of wound healing (as judged by tensile strength measurements and confirmed by the histologic observations) are very similar in the anemic, the milk-plus-iron control, and the chow weight control animals. Analysis of the data by the Fisher "t" test reveals that there are no statistically significant differences between the mean of the tensile strengths of the wounds in these groups (Table I). On the other hand, the tensile strengths of the wounds of the chow age controls were significantly higher on all days observed than those in any of the other groups.

Histologic examination of the wounds limited to one or two sections for each animal stained with hematoxylin-eosin disclosed the following findings: No significant changes were seen among the wounds of the first three groups (anemic milk-fed, nonanemic milk-and-iron-fed, and chow-fed size controls). In particular, in the anemic animals there was no delay in proliferation and

maturation of fibroblasts and in the appearance of mature collagen as judged by hematoxylin-eosin stains only. In the fourth group (chow-fed age controls) a greater amount of vascularization and granulation tissue was found.

TABLE I. TENSILE STRENGTH OF LAPAROTOMY WOUNDS IN ALBINO RATS

The p values for significance of the differences between the means of tensile strength of anemic milk-fed, nonanemic milk-and-iron-fed, and nonanemic chow-fed age and weight control rats.

POSTOPERATIVE DAY	p VALUES					
	GROUP A* & B†	GROUP A & C‡	GROUP B & C	GROUP A & D§	GROUP B & D	GROUP C & D
3	0.5	0.4	0.8	0.005	0.001	0.001
5	1.0	0.1	0.2	0.001	0.001	0.001
7	0.4	0.2	0.4	--	--	--
9	0.6	0.3	0.6	0.001	0.01	0.02
11	0.8	--	--	--	--	--

*Group A: Anemic milk-fed (41 rats).
†Group B: Nonanemic, milk-and-iron-fed (42 rats).
‡Group C: Chow-fed weight controls (26 rats).
§Group D: Chow-fed age controls (30 rats).

DISCUSSION

By the simple expedients of feeding rats exclusively on milk from the day of weaning, keeping them in iron cages which had been sprayed with aluminum paint and varnished, and allowing them only distilled water to drink, a progressive anemia reaching levels in the range of 5 to 7 Gm. of hemoglobin per 100 ml. of blood was produced in one to two months.

There is no doubt that the anemic animals suffered more than a simple nutritional milk anemia and that the milk-and-iron controls were not normal animals, since, although their hemoglobin and serum proteins were normal, they gained weight more slowly than similar animals fed on commercial rat chow. No differences were noted, however, in the animals with open wounds either in the time course of wound closure or in total healing time between the older milk-fed animals, both anemic and nonanemic, and their normal chow-fed controls. On the other hand, among the younger animals, wound closure after the fifth day tended to be more rapid in those fed chow than in the milk-fed groups ($p = 0.02$). This suggests that the milk diet, when supplemented with iron, is somewhat deficient from the point of view of healing of open wounds for the young growing rat, but is adequate for the full-grown animal. *In either case, however, the addition of a severe deficiency of hemoglobin, per se, did not influence the healing process.*

The apparent lack of influence of anemia upon the healing of open wounds is also seen in the healing of laparotomy incisions—no statistically significant differences were found among the mean tensile strengths of the wounds of the anemic, milk-plus-iron, and chow weight control rats. On the other hand, the wounds of the chow age controls were consistently significantly stronger than those of the other three groups. This would appear to be due principally to the extreme differences in weight, the chow age controls weighing at operation twice as much, on the average, as the animals in the other three groups. The microscopic appearances of the wounds confirmed the tensile strength findings.

It is conceivable that the healing of open wounds larger than those used in this study might be impaired in the presence of anemia, although the wounds were of not inconsiderable size (approximately 0.5 per cent of body surface) and the effect of age on wound healing was readily apparent. It might be anticipated, therefore, that if anemia had an important influence, it would have been apparent. Further, the size of the laparotomy incisions was considerable, corresponding in the human being to an incision extending from the xiphoid to midway between the umbilicus and symphysis. In a study of laparotomy incisions of similar size in rats, Kobak and associates[8] readily demonstrated the deterring influence of protein deficiency.

The present results are similar to the clinical impression of Levenson and associates[9] in regard to the healing of second degree burns in children with nutritional anemia and to the results reported by Besser and Ehrenhaft[2] in the healing of sutured stomach wounds in dogs with acute transient anemia consequent to venesection. They are, on the other hand, contrary to the results of Sandblom[13] and Sako and associates.[12]

There are several possible explanations for the discrepancies. This report concerns the healing of wounds in albino rats, while both Sandblom and Sako followed the healing of incisions in rabbits. The difference, then, may be related to the species of the experimental animal. It is also possible that in the rabbit anemia predisposes to infection which in turn adversely affects wound healing. The rat, on the other hand, is very resistant to infection, and the anemic rats appeared no more susceptible to infection than the controls. Further, Sandblom, and Sako and associates, produced anemia by venesection while in the present study anemia was produced by dietary restriction, principally of iron. It should also be pointed out that Sandblom made observations at only one point in the healing curve, whereas the entire curve of healing was followed in the present study. The fact that these discrepancies are present serves as a warning against indiscriminate application of data obtained in one species of animal to other species or to man and argues against the assumption that factors operative in the healing of one type of wound necessarily apply to the healing of wounds of a different type.

SUMMARY

A marked, progressive, nutritional milk anemia was produced in albino rats maintained on an unsupplemented diet of ordinary pasteurized cows' milk. The healing of both open skin wounds and laparotomy incisions was studied in these animals and in suitable nonanemic controls (rats on milk-plus-iron diet, as well as rats on a commercial chow diet).

An initial lag period in the healing curve was not observed, although this has been described by others. Rather, there was contraction of the wound area within the first day, after which there was a brief (1 to 2 day) lag. Following this, wound closure proceeded rapidly until day 9, after which time the healing process slowed progressively until complete healing was reached. The healing of the laparotomy wounds was similar to that commonly described in the literature.

No evidence was found that anemia per se of severe degree, maintained for from 2 to 6 weeks prior to operation and throughout the postoperative period, exerts any influence, deleterious or otherwise, on the closure of open skin wounds or the healing of laparotomy wounds in the albino rat.

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HYPOTENSIVE ANESTHESIA IN RADICAL PELVIC AND ABDOMINAL SURGERY

C. Paul Boyan, M.D.,* and Alexander Brunschwig, M.D., New York, N. Y.

(From the Memorial Center for Cancer and Allied Diseases and the Sloan-Kettering Institute for Cancer Research)

THE hypotension in surgical shock is due to the reduction of the circulating blood volume and is accompanied by vasoconstriction. The latter represents the compensatory mechanism of the body acting to maintain adequate blood pressure levels. If not rectified by increase in the circulating blood volume, the continued vasoconstriction leads to tissue anoxia, which, if present for some time, results in irreversible damage to the cells with eventual death (irreversible shock).

Hypotension, per se, in the presence of normal blood volume is not a dangerous situation, within certain relatively wide limits of duration. Phemister and associates[1] showed that reduction of blood pressure in rabbits to 25 to 40 mm. Hg resulting from stimulation of the aortic depressor nerve could be maintained for a relatively prolonged period of time without leading to death, as compared to equal reduction in blood pressure due to hemorrhage. Dale and Laidlaw[2] demonstrated that a carefully adjusted venous infusion of acetylcholine in cats produced dilatation of the arterioles and lowering of the systolic blood pressure to 30 to 50 mm. Hg, the veins being well filled and the venous return to the heart remaining practically normal.

In 1946 Gardner[3] reported the induction of relative hypotension in a patient preoperatively by withdrawing 1,600 c.c. of blood from the dorsalis pedis artery and later reinfusing 1,100 c.c. after the operation. The operation was excision of a meningioma of the olfactory groove, and it was his impression that hemorrhage in the operative field was reduced and the procedure thereby facilitated. The blood pressure was lowered from 140 mm. Hg to 100 mm. Hg systolic. In this situation, however, a certain degree of vasoconstriction must have occurred.

Theoretically, the principle of induced hypotension to reduce loss of blood from the operative field, would appear to be a sound one, providing such hypotension be brought about by arteriolar dilatation and without loss of circulating blood volume.

Griffiths and Gillies[4] reported upon "controlled hypotension" induced by high spinal block with sympathetic paralysis (arteriolar dilatation) to reduce bleeding in thoracolumbar splanchnicectomy and sympathectomy.

In 1948, Paton and Zaimis[5] reported upon the ganglionic blocking properties of the penta and hexamethonium halides. Such paralysis of sympathetic ganglia interrupted the efferent vasoconstrictor nervous impulses resulting in

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*Department of Anesthesiology, Memorial Center for Cancer and Allied Diseases.

arteriolar dilatation and fall in the blood pressure. These agents are now under trial in the treatment of hypertension.

In 1950 Enderby[6] described his method of "controlled circulation." He used pentamethonium bromide as a hypotensive drug and carried out appropriate posturing of the patient to pool the blood away from the operative field. In addition other British anesthesiologists have employed these agents to induce hypotension and reduce bleeding in a variety of operations: Shackleton[7]—plastic procedures on the head and neck, Hughes[8]—fenestration operations, Lewis[9]—thoracic operations.

It occurred to one of us (A. B.) that, in the complicated and extensive operations for advanced pelvic and abdominal cancer, controlled hypotension under anesthesia might well be worth a trial to reduce bleeding from the extensive raw surfaces, facilitate the operative procedures, and reduce substantially the quantity of blood to be transfused.

This report is concerned with the experiences gained in a series of 32 patients. It would appear that until the present, hypotensive anesthesia has not been reported in a series of very radical excisive procedures within the pelvis and the abdomen of the magnitude described here. All the anesthetics were administered by one of us (P. B.); a type of hypotensive anesthesia produced by injection of hexamethonium bromide (C_6),* a ganglionic blocking agent, and postural ischemia combined with Pentothal Sodium-d-Tubocurarine-ether-oxygen anesthesia is described.

TECHNIQUE OF HYPOTENSIVE ANESTHESIA

The patient is carefully premedicated in the usual way with morphine and scopolamine or atropine, in doses according to age and physical status, 60 to 90 minutes before the scheduled time of operation. Upon placing the patient on the table the pulse, blood pressure, and respiratory rate are recorded. A 15 gauge needle is securely introduced into an accessible arm vein and a three-way stopcock is attached to permit the alternative administration of blood, saline, or Pentothal Sodium solution without delay. The patient is intubated under 2.5 per cent Pentothal Sodium supplemented by 8 to 15 mg. of d-Tubocurarine chloride. The tube is passed by the oral or nasal route under direct vision and ether is administered by the closed absorption method. Then the patient is examined, prepared, and draped. By that time about 20 to 30 c.c. of ether has been inhaled. A blood pressure reading is taken to determine the response to the anesthetic agents. The degree of fall, if any, will indicate the initial dose of C_6. If the difference is not greater than 20 mm. Hg, 20 to 40 mg. of C_6 are injected into the intravenous tubing. In cases showing a greater fall of systolic pressure, not more than 15 to 20 mg. of C_6 are given as an initial dose. The patient then is placed in approximately a 30° Trendelenburg, or supine jackknife, position. Within 3 to 5 minutes the systolic blood pressure usually falls to 50 to 70 mm. Hg. If this does not occur, additional doses, of not more than 20 mg. of C_6 at a time, are given at intervals of 5 min-

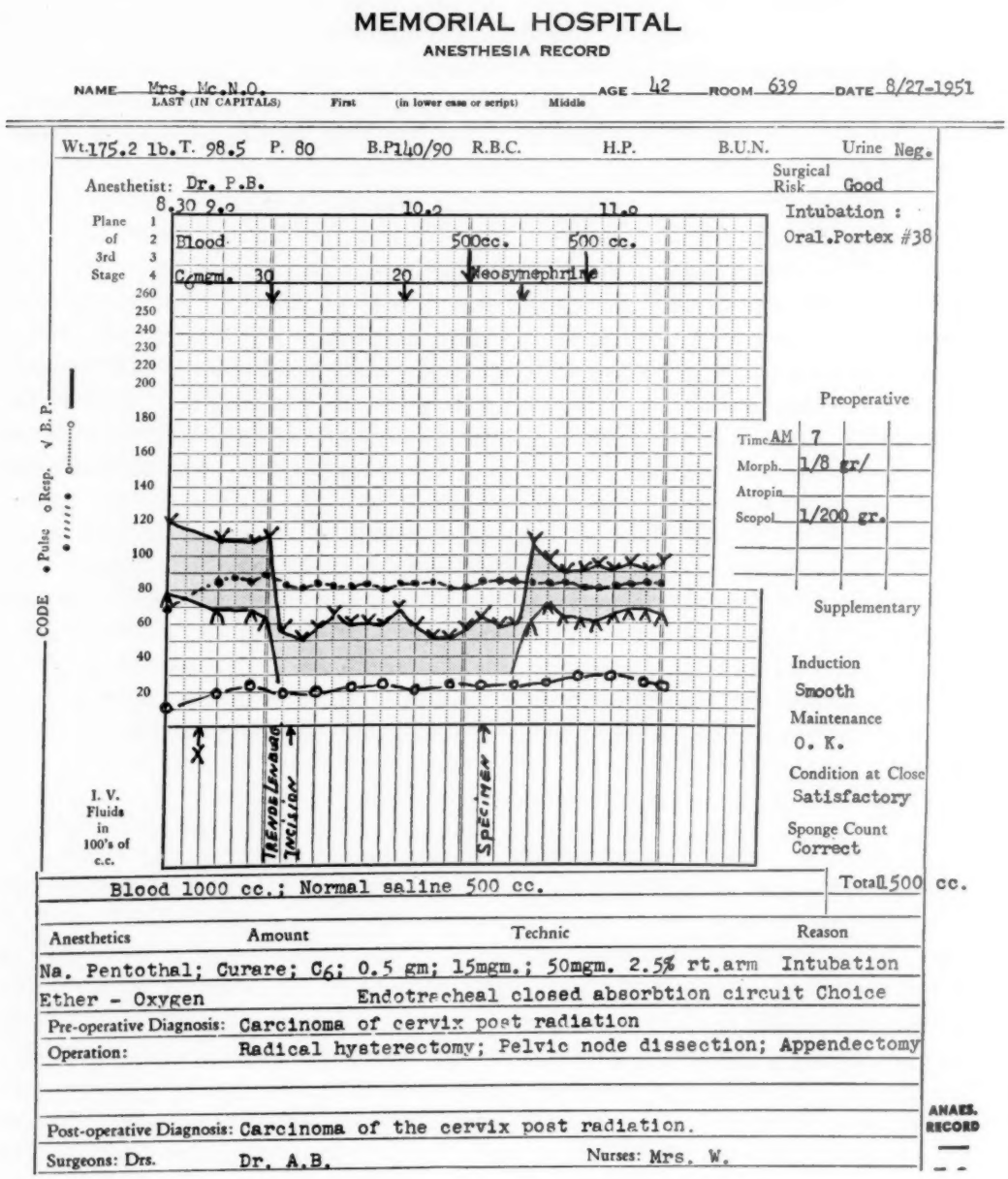
*Hexamethonium bromide is known as C_6. It was supplied by Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y., for these studies, and the authors wish to acknowledge their cooperation.

utes until the desired low level is reached. The optimum is between 55 and 65 systolic. The blood pressure often cannot be taken by the auscultation method, but the palpation or oscillation methods, with the necessary correction, are successful. The pulse, if not palpable on the radial or temporary artery, is always perceptible at the carotid artery. The respirations must be closely observed since they may be easily influenced by the depth of anesthesia and other factors, for example, tight abdominal packing, excessive Trendelenburg position, etc. If the tidal exchange has diminished somewhat assisted respiration is applied. The patient is noted to be pink and warm. The capillary refilling time on the forehead or ear is a good index of the peripheral circulation. The blood loss is estimated and immediately replaced. The systolic blood pressure remains at a low level for various periods of time. Usually, after 30 to 60 minutes, the pressure is noted to rise slowly. If the required excisional surgery goes beyond this period, additional quantities of C_6 are administered. Before closure of the abdomen, the systolic blood pressure is returned to almost normal level by the infusion of a dilute solution of Neo-Synephrine (10 mg. in 500 c.c. 5 per cent glucose in water). The response is immediate and enables the surgeon to clamp and ligate any vessels which did not bleed during the hypotensive state. For the abdominal closure the Trendelenburg position is reduced and the legs are returned to horizontal. Additional small amounts of ether are given as deemed necessary to facilitate the closure of the abdominal wall. At the conclusion of the operation, the endotracheal tube is removed after a thorough tracheobronchial toilet. The patient is then transferred gently to the bed and the legs are elevated. A minimum systolic blood pressure of about 100 mm. Hg should be maintained with Neo-Synephrine drip, if necessary. During the recovery period the patient must be under constant supervision, and the blood pressure taken every ten minutes. After it has been stabilized, the legs are gradually lowered and the head is elevated on a pillow. The other immediate postoperative care does not differ from the usual routine for major surgical cases. Figs. 1 and 2 represent typical records of hypotensive anesthesia.

RESULTS

This report is based on a series of 32 patients: 4 men and 28 women. The patient's age, type and duration of operation, normal blood pressure, degree and period of hypotension, blood replacement, quantity of C_6 administered, and the degree of ischemia in the operative field are given in Table I. The anesthesia in all instances was satisfactory. The pupils of most of the patients were dilated. The pulse rate did not show significant change and remained the same during the hypotensive state with variations of ±15 beats from the pre-anesthetic level. Two patients had an increase of 20 beats, that is to 110 and 120 respectively. In one patient, the blood pressure could not be obtained for 25 minutes. Two patients had 40 to 50 mm. Hg systolic blood pressure for 100 and 60 minutes respectively. Venous pressure readings determined in 13 patients showed no deviation of significance from those of normotensive cases. Electrocardiograms were done on 17 patients before and after hypotensive anes-

thesia; these were comparable to the findings in patients submitted to similar operative procedures in normotensive state. The urinary output was measured in all cases for the first 5 postoperative days; there was no deviation from the records of control patients. The recovery time from anesthesia was not prolonged and the incidence of vomiting seemed reduced. Postoperative hemorrhage of significance was not encountered. One patient was given 1,000 c.c. of blood and two other patients each received 500 c.c. during the immediate postoperative



MEMORIAL HOSPITAL

ANESTHESIA RECORD

NAME Mrs. Mc.N.O. (LAST (IN CAPITALS) First (in lower case or script) Middle) AGE 42 ROOM 639 DATE 8/27-1951

Wt. 175.2 lb. T. 98.5 P. 80 B.P. 140/90 R.B.C. H.P. B.U.N. Urine Neg.

Anesthetist: Dr. P.B. Surgical Risk Good

Intubation : Oral. Portex #38

Plane of 3rd Stage 1 2 3 4

8.30 9.0 10.0 11.0

Blood 500cc. 500 cc.

C6 mgm. 30 20 Neosynephrine

CODE • Pulse o Resp. √ B.P.

260 250 240 230 220 200 180 160 140 120 100 80 60 40 20

Preoperative

Time AM 7

Morph. 1/8 gr/

Atropin

Scopol 1/200 gr.

Supplementary

Induction Smooth

Maintenance O. K.

Condition at Close Satisfactory

Sponge Count Correct

I. V. Fluids in 100's of c.c.

X TREVOR LEVAGE INCISION SPECIMEN

Blood 1000 cc.; Normal saline 500 cc. Total 1500 cc.

Anesthetics	Amount	Technic	Reason
Na. Pentothal; Curare; C6;	0.5 gm; 15mgm.; 50mgm.	2.5% rt.arm	Intubation
Ether - Oxygen		Endotracheal closed absorbtion circuit	Choice

Pre-operative Diagnosis: Carcinoma of cervix post radiation

Operation: Radical hysterectomy; Pelvic node dissection; Appendectomy

Post-operative Diagnosis: Carcinoma of the cervix post radiation.

Surgeons: Drs. Dr. A.B. Nurses: Mrs. W.

ANAES. RECORD

Fig. 1.—Anesthesia record for Case 14 (N. O.). Radical hysterectomy and pelvic node excision. Note precipitous fall in systolic blood pressure to 50 to 60 mm. Hg, which lasted for 1 hour and 15 minutes due to injection of C_6. Pulse and respirations remained steady. Total blood infused was 1,000 c.c.

period. Five patients developed minimal pulmonary atelectasis and another had pneumonia with transient cardiac irregularities. One patient developed thrombophlebitis of a mild degree in the right calf. In two of the early cases, the blood pressure was unstable postoperatively and necessitated administration of Neo-Synephrine drip intermittently during a period of a few hours. One of these patients received 100 mg. of C_6 without a fall of blood pressure below

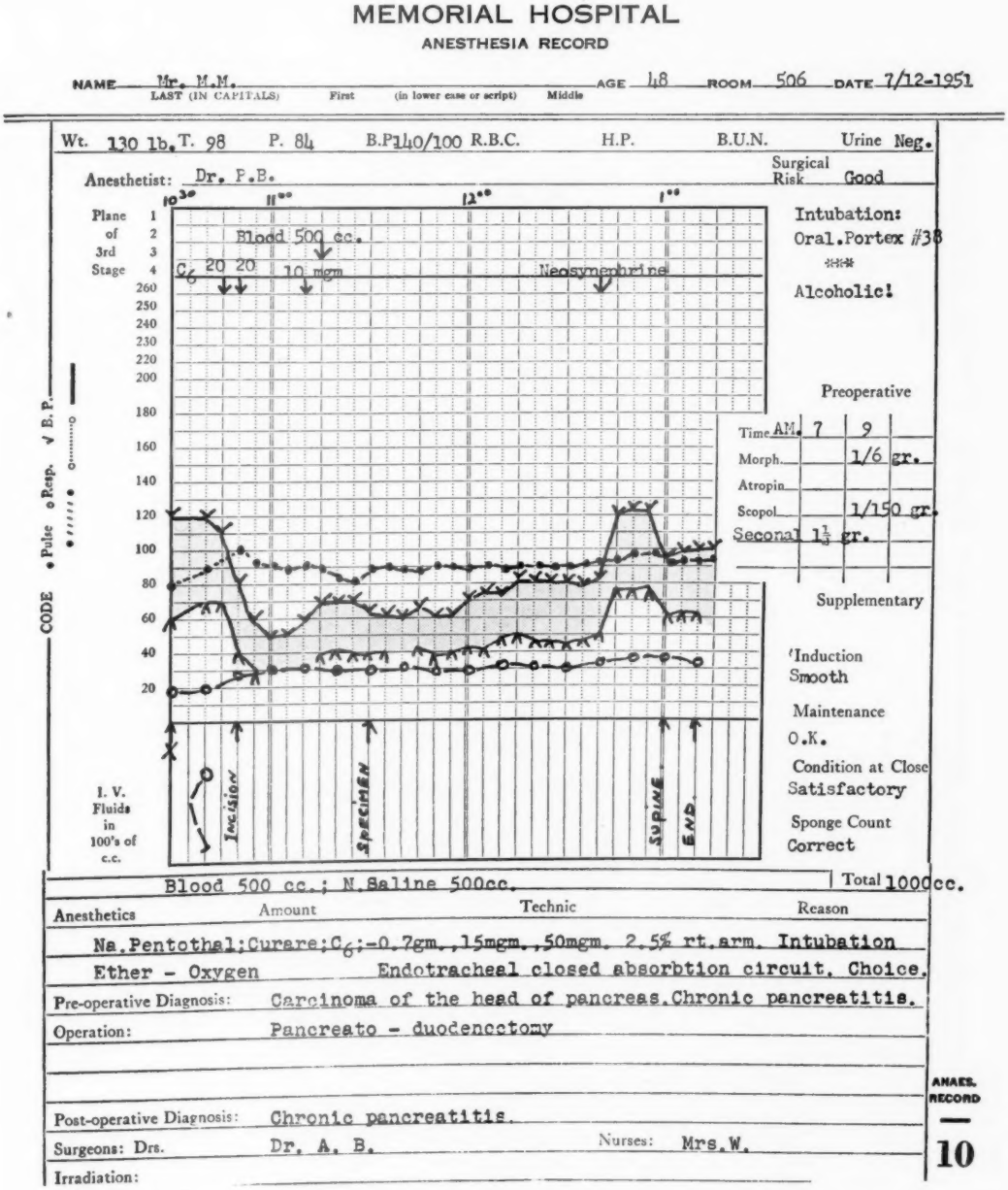


Fig. 2.—Anesthesia record for Case 3 (M. M.). Pancreatoduodenectomy for lesion of head of pancreas, thought to be carcinoma, but later proved to be pancreatitis. Note precipitous fall in blood pressure at onset of operation to 50/30 and subsequent gradual elevation to 80/40, finally rising to 120/80 after administration of Neo-Synephrine. Total blood infused was 500 c.c.

TABLE I. SUMMARY OF PERTINENT DATA IN 32 PATIENTS SUBJECTED TO HYPOTENSIVE ANESTHESIA

PATIENT	AGE	SEX	TYPE OF OPERATION	DURATION OF OPERATION (IN MINUTES)	NORMAL BLOOD PRESSURE (IN MM. HG)	DEGREE OF HYPOTENSION (SYSTOLIC BLOOD PRESSURE)	DURATION OF HYPOTENSION (IN MINUTES)	BLOOD TRANSFUSION (IN C.C.)	HEXAMETHONIUM BROMIDE GIVEN (IN MG.)	DEGREE OF ISCHEMIA IN THE OPERATIVE FIELD
1. M. P.	60	M	Total pelvic exenteration; wet colostomy	120	130/80	55 to 75	60	1,000	40	Excellent
2. J. P.	42	F	Total pelvic exenteration; rt. nephrectomy; resection of small bowel; jejunocecostomy; wet colostomy	160	120/60	40	60	2,500	20	Excellent
3. M. M.	48	M	Pancreatoduodenectomy	140	148/90	50 to 80	100	500	50	Excellent
4. L. B.	47	F	Resection of sigmoid and loop of small bowel; partial resection of bladder; radical hysterectomy; appendectomy	210	132/84	60 to 75	55	2,000	60	Excellent
5. L. R.	41	F	Total pelvic exenteration; wet colostomy; appendectomy	155	150/90	60 to 85	75	3,000	120	Very good
6. U. N.	40	F	Total pelvic exenteration; colostomy; bilateral cutaneous ureterostomies	125	120/80	68 to 80	50	1,000	80	Excellent
7. T. D.	30	F	Exploratory laparotomy; presacral neurectomy; biopsy	90	122/80	85	35	none	40	Undetermined
8. R. B.	28	F	Abdominoperineal radical hysterectomy and pelvic node dissection; appendectomy	110	140/80	60 to 70	60	1,500	40	Good
9. G. E.	55	F	Radical hysterectomy and pelvic node dissection	115	150/90	50 to 75	60	1,000	60	Excellent
10. M. M.	57	F	Radical vulvectomy; left pelvic and groin node dissection; liver biopsy	215	130/85	0 to 60	45	500	20	Excellent
11. F. L.	31	F	Radical hysterectomy and pelvic node dissection; liver biopsy; appendectomy	110	102/50	80 to 100	15	1,000	100	None observed
12. P. E.	59	F	Abdominoperineal radical hysterectomy and pelvic node dissection; resection of bladder; ureterosigmoidostomies	195	140/100	40 to 60	100	1,000	40	Excellent
13. A. H.	41	F	Total vaginectomy and pelvic node dissection; repair of bladder; suprapubic cystotomy; appendectomy	110	144/60	60 to 80	75	500	40	Excellent
14. N. O.	42	F	Radical hysterectomy and pelvic node dissection; appendectomy	110	140/90	55 to 70	70	1,000	50	Excellent
15. O. M.	48	F	Radical hysterectomy and pelvic node dissection	220	130/85	60 to 70	120	2,500	60	Very good
16. V. R.	50	M	Exploratory laparotomy; liver biopsy	75	115/30	65	15	none	90	Undetermined

17. S. E.	46	F	Abdominoperineal radical hysterectomy	110	118/84	70 to 90	60	500	40	Very good
18. G. E.	40	F	Abdominoperineal radical hysterectomy and pelvic node dissection; appendectomy; suprapubic cystostomy	150	128/82	70 to 90	75	1,500	40	Excellent
19. P. E.	20	F	Excision of cervical stump; rt. salpingo-oophorectomy; appendectomy	65	120/80	75 to 90	30	500	30	Questionable
20. S. C.	49	F	Radical hysterectomy and pelvic node dissection	110	132/88	50 to 80	45	1,500	20	Good
21. B. W.	57	M	Exploratory laparotomy; biopsy cholecystojejunostomy	70	136/82	62 to 85	60	none	40	Excellent
22. N. A.	54	F	Exploratory laparotomy; rt. nephrectomy; attempt to excise a large tumor	100	136/80	70 to 90	45	3,000	40	Questionable
23. M. E.	40	F	Excision recurrent ca. pelvic wall; resection ext. iliac artery and vein right; transection rt. ureter and ureterosigmoidostomy	110	120/70	0 50 to 70	5 55	3,500	80	Excellent
24. R. A.	44	F	Abdominoperineal radical hysterectomy; pelvic node dissection; bladder repair; appendectomy	75	128/80	60 to 78	50	2,500	80	Good
25. B. O.	36	F	Radical hysterectomy and pelvic node dissection; appendectomy	130	130/85	85	10	1,500	60	None observed
26. E. R.	53	F	Radical hysterectomy and pelvic node dissection; abdominoperineal resection of rectum; colostomy	285	142/80	60 to 80	150	3,000	50	Very good
27. D. E.	47	F	Sigmoidocolectomy; periaortic node dissection; bilateral salpingo-oophorectomy; appendectomy	120	130/90	50 to 70	80	1,000	40	Excellent
28. C. E.	53	F	Radical hysterectomy and pelvic node dissection; appendectomy	195	115/85	70 to 90	65	2,500	90	Good
29. B. A.	54	F	Excision cervical stump and pelvic node dissection	135	160/80	70 to 85	75	1,000	40	Good
30. B. H.	48	F	Abdominoperineal vaginectomy and radical hysterectomy; appendectomy	120	150/88	55 to 65	55	1,500	40	Excellent
31. S. T.	45	F	Exploratory laparotomy; biopsy; resection of rectosigmoid and end-to-end anastomosis; colostomy	60	110/90	68 to 78	38	none	50	Very good
32. T. S.	34	F	Multiple myomectomies; excision ovarian cyst; liver biopsy	90	120/75	60 to 70	20	none	100	Good

100 mm. Hg for longer than 10 to 15 minutes during the operation. The hypotension occurred on the ward after the operation was completed. Another patient failed to respond to the administration of 60 mg. of C_6. In 29 patients where excisional surgery was carried out the average amount of blood transfused was 1,500 c.c. per operation, with extremes of 0 to 3,500 c.c. The mental status of all patients was carefully checked and there were no detectable changes postoperatively.

DISCUSSION

In hypotensive anesthesia there are several problems which require further investigation before its application can be endorsed. The oxygenation of the brain is of prime importance. All clinical signs indicated that there is no impairment, in that the patients remained pink in color and the capillary refilling time on the forehead was brisk. It was noted that the abdominal viscera, which, in the Trendelenburg position, are at a level higher than the brain, showed good oxygenation. This also strongly suggested that the brain in its dependent position did not suffer from anoxia. Hafkenschiel and associates[10] reported that cerebral blood flow and oxygen uptake were essentially unchanged when the mean arterial blood pressure was significantly reduced with dihydroergocornine.

In order to fulfill one of the postulates for hypotensive anesthesia, good oxygenation of the blood, a patent airway was insured by endotracheal intubation and close observation of rate and depth of respiration. The absence of any degree of cyanosis in all cases showed that the desired oxygenation was easily maintained. The blocking effect of hexamethonium bromide does not bring about the respiratory muscle paralysis which occurs sometimes with the high spinal block and would seem to be more physiologic than the latter in producing hypotension. There is clinical evidence that C_6 has a mild curarelike action as shown by the abdominal muscle relaxation which was better when C_6 was added in the course of anesthesia than that produced by Pentothal-curare-ether method only.

As stated, most of the procedures carried out were of more than usual magnitude and there was a certain quantity of blood lost, which required immediate blood replacement in order to fulfill the main postulate of hypotensive anesthesia, namely, unreduced circulating blood volume. Dr. Virginia K. Pierce had the responsibility for supervising this by weighing sponges and laparotomy pads, and noting content of the suction bottles. At the same time continuous venous pressure readings were taken to aid in determining the adequacy and the required rate of blood replacement. This constitutes a separate study and will be reported subsequently by Pierce, Boyan, and Masterson. The venous pressure during the hypotensive state revealed no deviation from the normotensive anesthesia which indicates adequate venous return to the heart. That the rate and quality of the pulse did not show changes of significance is an indication of sufficient and unimpaired cardiac function. The impression at operation was that the bleeding from small vessels was practically nil while larger ones appeared more prominent thus facilitating their isolation, clamping, and ligation. On several occasions large veins (external and common iliac veins and inferior vena cava) were inadvertently opened, but the bleeding could be easily controlled.

The excretion of urine will cease at a systolic pressure below 75 mm. Hg, but when the arterioles are dilated, a lower pressure head may be sufficient to give the necessary filtration pressure. In any case, the renal parenchyma does not suffer during this type of hypotension; a conclusion based at the present upon clinical results only. There was no oliguria or anuria of significance in the postoperative course of the cases in this series. It is important to bear in mind the fact that the capillary pressure at the arterial side is about 32 mm. Hg and that a systolic pressure below 40 mm. Hg for a longer period might possibly impair the capillary circulation, thereby jeopardizing tissue metabolism.

The patients in this series were selected for unimpaired cardiovascular function. In the beginning we were strict in our requirements, but as experience was gained, cases of mild hypertension and arteriosclerosis were also included.

The use of proper premedication should be stressed. Individuals not well sedated were noted to require larger amounts of C_6 to produce the desired hypotension; the two patients who did not respond to C_6 were premedicated shortly before coming to the operating room and both were very apprehensive individuals. It was probably a matter of coincidence that both "failures" were Negroes. It is possible that the nervous stress in these individuals produced outpouring of adrenaline which counteracted the administered C_6. Our impression is that if the systolic blood pressure does not fall with the first 20 to 60 mg. of C_6, further administration would not give a satisfactory result. The patients may be divided into two categories according to their response to hexamethonium bromide. The first group includes those individuals who require larger doses with variable response in blood pressure decline; this was noted more commonly in the younger age group. The second group, mostly middle-aged patients, responded satisfactorily to small doses of the medication.

The hypotensive state should be maintained as long as it is necessary to remove the specimen and secure the hemostasis. At the present time, our desire is not to exceed 75 to 100 minutes with low systolic pressure of 45 to 65 mm. Hg. When the blood pressure was returned nearly to normal before closing the abdomen, it was found that there were few bleeding points not previously noted during the hypotensive state. Apparently the time interval of hypotension was such that clotting occurred in those vessels. Dislodgment of clots by vigorous sponging of the operative field defeats this mechanism.

The immediate postoperative period requires close supervision by experienced personnel to differentiate between internal hemorrhage with a drop in blood pressure and a prolonged response to C_6 administration. Obviously, bleeding will not be controlled by Neo-Synephrine drip; conversely, the injudicious use of blood during this period could result in cardiac embarrassment. The elevation of the legs aids mechanically in maintaining the blood pressure at the desired level and often was the only measure applied.

The infrequent occurrence of venous thrombosis in the legs of these patients is of interest and importance. The Trendelenburg position used for the pelvic surgery in this group is one in which the legs were flexed and, without the use of shoulder braces, the weight of the body was borne by them. The

low incidence of venous thrombosis in the legs would appear to be an indication of adequate blood circulation during the hypotensive state. Supine jackknife position was employed for the operative procedures in the upper abdomen.

During this type of anesthesia, the anesthesiologist must be constantly on the alert to observe the proper oxygenation and the changes in the blood pressure and pulse, and to watch blood loss and maintain proper replacement.

With extensive surgical operations now frequently and successfully being carried out with current methods of anesthesia the question may be raised as to whether hypotensive anesthesia is worth the extra effort and vigilance necessary. Certainly there is no special indication for it in the usual types of operations. However, in very radical procedures for extensive neoplastic diseases it is well worth further investigation.

SUMMARY

A report is presented of an initial experience with 32 patients, most of whom were subjected to more than usually radical operations for abdominal and gynecological cancer and in whom a controlled hypotensive state was induced by means of hexamethonium bromide (ganglionic blocking agent) and "postural ischemia" under general anesthesia.

It is the very distinct impression that these operations were appreciably facilitated and the blood loss reduced as a result of the hypotensive anesthesia.

ADDENDUM

Twenty additional patients have been operated upon satisfactorily since this report was submitted. These operations included partial hepatectomy, thoracoabdominal gastroesophagectomy, etc.

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DELAYED ONSET OF SYMPTOMS DUE TO EXTRADURAL HEMATOMAS

ARTHUR B. KING, M.D.,* SAYRE, PA., AND
JOHN W. CHAMBERS, M.D., BALTIMORE, MD.

THE experience of surgeons, which has now become the accepted theory of medical textbooks, teaches that extradural hematomas are acute tumors, and that symptoms become manifest within a few hours after trauma. However, from time to time, authors reviewing series of cases have noted that in occasional instances the onset of symptoms may be delayed for long periods. Patients may survive for days and die without the diagnosis having been made. This was the experience of Moody,[9] who reviewed a large number of cases. The longest survival in his series was twelve days, the patient dying without operation. He noted that those patients who came to operation were usually operated upon within twelve hours but that occasionally patients did not show sufficient symptoms to suggest the condition for several days, the longest interval before the development of symptoms being seven days. During our own experience, covering a period of several years, we have encountered several instances of large extradural hematomas that have not presented sufficient signs and symptoms for twenty-four hours after injury to warrant surgical exploration. We should like to point out, however, that no matter when such signs do appear, an emergency operation is necessary to save the patient's life.

CASE 1.—J. S. (JHH 333384), a 38-year-old white man, was hit in the mouth, fell, and struck his head. He was examined shortly thereafter and was considered intoxicated. Recovery was prompt, so he was discharged a few hours later. After his discharge there were complaints by his family that he was "crazy," irrational, and disoriented, wandering in the streets clad in pajamas, etc. The patient was drowsy, complained of headaches, and vomited frequently. Eleven days after the accident he was admitted to the hospital because of the bizarre behavior.

Physical examination disclosed a drowsy, incoherent, disoriented white man who staggered markedly on walking. Early bilateral papilledema was present. X-rays of the skull disclosed a linear fracture in the right temporoparietal region, and the pineal gland was shifted to the left. Trephines were used in the frontal and temporal regions but no blood was found. A ventriculogram showed a shift to the left and the posterior part of the right lateral ventricle was pushed downward.

A right-sided bone flap was turned down over the parietal region. A solid extradural hematoma was encountered which was about 7 mm. thick and about 150 c.c. in volume. After removal of this hematoma, the underlying dura was found to be blue and tense. When incised, a subdural hematoma of about 100 c.c. was evacuated. The source of the bleeding of the extradural hematoma was not determined, but the operator thought it was venous.

Recovery was immediate and uneventful except for the mental confusion which lasted for a month. Later on, osteomyelitis of the bone flap developed, but was neglected. When the patient was seen one year later, removal of the flap was carried out with permanent cure resulting.

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*Formerly Resident Neurosurgeon, The Johns Hopkins Hospital.

CASE 2.—C. F. (JHH 412568), a 39-year-old Negro man, fell and struck his head on January 1. He was hospitalized elsewhere for eight days and was told that he had a fractured skull. The patient complained of headaches for a few days. After discharge from the hospital he returned to work.

On February 6, a second fall occurred and a slight scalp wound was sustained. There was no disturbance of consciousness. Shortly thereafter, he developed severe left-sided headaches and pain behind the eyes. The patient became drowsy and nauseated. Because of increasing drowsiness he was admitted to the hospital, three days after the second fall.

Examination found the patient conscious but lethargic. He talked slowly but clearly. The entire head was tender to percussion. A healed scar on the left forehead, due to the first injury, was noted, as well as a small recent laceration in the left parietal region.

The pulse rate was 60 and respirations were 16 per minute. The left knee and ankle reflexes were hyperactive. Bilateral unsustained clonus was noted. X-rays of the skull revealed a fracture in the left parietal region.

Because of an increasing bradycardia with a pulse rate of 48 to 52 per minute, frontal trephines were carried out on February 11, five days after the second accident and forty-two days after the first accident. Nothing was found, so a ventriculogram was done. The lateral ventricles were shifted to the right. The third ventricle was oblique, and the posterior portion of the left lateral ventricle was depressed.

A bone flap was elevated in the parieto-occipital region. A thick, solid, old extradural hematoma, about 100 c.c. in volume, was found, extending toward the torcular Herophili. No bleeding points were found but the operator felt the blood came from the dural sinuses in the region of the torcular Herophili. Recovery was uneventful.

CASE 3.—P. B. (JHH 363430), a 16-month-old white boy, fell out of his chair and struck the right side of his head on a sharp object four days before admission to the hospital. The child was unconscious for approximately four hours and during this time had several convulsions. When consciousness returned, a left hemiparesis was noted. Since the accident, the baby had been vomiting and the paralysis had persisted.

When examined, bulging of the scalp in the right parietal region was found. The hemiplegia on the left was now complete. X-rays of the head disclosed a fracture of the calvarium on the right, parallel to the superior longitudinal sinus. A bone flap was reflected and a huge solid extradural hematoma was found covering the entire right cerebral hemisphere. It was thought the bleeding had come from the longitudinal sinuses.

The postoperative course was very unsatisfactory. Hyperthermia, convulsions, and tremendous intracranial pressure followed, which necessitated removal of the bone flap. Unconsciousness was prolonged. Later the child showed marked mental retardation, bilateral spasticity, hyperreflexia, frequent convulsions and poor voluntary movement of all extremities. One year after operation the child could not stand, talk, or follow a light. Convulsions occurred frequently.

CASE 4.—R. E. (JHH 436118), a 21-year-old white man, was struck by a car and brought to the hospital within a few minutes in an unconscious state. He soon roused, vomited several times, and became combative. Within an hour, ecchymosis of the right eyelid appeared, indicating a fracture of the skull.

The patient was admitted for observation. The state of consciousness remained cloudy. Blood was noticed behind the right eardrum. An equivocal Babinski response appeared on the left.

During the next three days the pulse rate fell steadily from 80 to 60 per minute and the respiration rate from 40 to 18 per minute. Edema of the scalp over the right frontal and temporal regions appeared. About seventy-two hours after the accident, the right pupil became dilated and fixed to light.

At operation a huge right-sided extradural hematoma was found. The middle meningeal artery was torn, but bleeding had ceased spontaneously. Recovery was uneventful.

CASE 5.—P. N. (JHH 302065), an 8-year-old white boy, while alighting from a street car, was struck by a car. He was unconscious for about ten minutes. After being observed at the hospital for four and one-half hours, he was discharged. The child had a lucid interval

during which he was normally active for twenty-one hours. Within a few hours he became drowsy and vomited, and his pulse rate rapidly fell.

At examination on readmission twenty-four hours after the accident, the pulse rate was 54 per minute, the right pupil was dilated and fixed to light, a left hemiparesis was present, the state of consciousness was described as stuporous, and tonic spasms were noted. X-rays of the skull taken while the child was on the way to the operating room failed to disclose a fracture. A large extradural hematoma was evacuated from the right side. The source of bleeding was the posterior branch of the middle meningeal artery. Recovery was uneventful.

CASE 6.—C. J. (JHH 236704), a 16-year-old Negro boy, ran into the back of an automobile while riding a bicycle, striking the left side of the forehead. He was unconscious for only a few minutes. The laceration was sutured. For the next four days he complained of frontal headaches, vomited on several occasions, and slept more than usual.

On the fifth day after the accident he was admitted to the hospital because of increasing drowsiness. The pulse rate was 54 and respirations were 16 per minute. Skull x-rays showed a depressed comminuted fracture about the size of a fifty-cent piece in the left frontal bone, near the hairline.

The laceration was reopened, and the fragments removed. An extradural hematoma over 150 c.c. in volume was encountered and removed. The dura was intact and no source of bleeding was found.

The postoperative course was uneventful.

CASE 7.—A. F. (Mercy Hospital 80654), a 12-year-old white boy, while playing baseball was struck on the left side of the head with the bat. He was not knocked unconscious. Twenty-four hours after the accident, he complained of a headache and vomited his supper. On the following morning he could not be roused.

When examined forty-eight hours after the accident, the child was stuporous, responding only to pain. The left pupil was dilated and fixed to light. Weakness of the right arm and leg was noted, as well as bilateral dorsiflexion of the great toes on plantar stimulation. X-rays of the skull failed to disclose any abnormalities.

At operation, a large extradural hematoma was removed from over the anterior portion of the left cerebral hemisphere. Several branches of the middle meningeal artery appeared to have been torn, but bleeding had ceased spontaneously. The postoperative course was uneventful but all the neurological signs did not disappear until three weeks later.

CASE 8.—K. S. (Perry Point Veterans Administration Hospital 16936), a 21-year-old white man, was involved in a fight during the night of October 29. The following morning he was very drowsy and vomited.

When admitted to the hospital on the morning of October 30, the patient was incontinent and roused only to painful stimuli. The temperature, pulse, respiration rate, and blood pressure were all within normal limits. A laceration over the left parietal region was found and there was swelling and discoloration of the scalp over the temporal bone. The neck was stiff. Except for the state of consciousness, the neurological examination was negative. Skull x-rays revealed a linear fracture in the left temporal region.

Improvement in consciousness was steady and by November 1, about sixty hours after the trauma, the patient was sitting up in bed smoking and eating. Shortly thereafter, a generalized convulsion ensued. The left pupil became dilated and fixed to light, followed shortly by dilation of the right pupil. Bilateral clonus and extensorplantar reflexes were found. Tonic spasms started a few minutes later.

Trephines were done immediately, and a large extradural hematoma about 3 cm. thick was removed from over the posterior half of the left cerebral hemisphere. There was an adherent clot over the posterior branch of the middle meningeal artery. The dura was opened and a small amount of blood was found in the subdural and subarachnoid spaces. The ventricles were tapped and blood-tinged fluid was recovered.

The postoperative course was complicated by hyperthermia, empyema, and a lung abscess. These resolved, but a right homonomous hemianopsia persisted.

DISCUSSION

In the extensive literature that is available on extradural hematomas, emphasis is placed on the arterial source of bleeding, and the presence of symptoms within a few hours of trauma. Vance,[13] in a detailed study of the results of head injuries, stresses these points. However, he did remark that extradural hemorrhages might be venous in origin. He stated that such hematomas were generally smaller in weight than the usual arterial variety but that clinical symptoms did not parallel the size of the clot.

It is often assumed that the dura is stripped from the bone by pressure of the arterial blood, producing the extradural hematoma. This explanation fails to account for the venous collections of blood. Verbrugghen[14] emphasized that the dura was separated from the skull at the time of the blow and that blood could then escape into the space thus formed (first postulated by Sir Charles Bell).

Two papers appeared in 1941 in which the venous variety of hematoma was discussed. Munro and Maltby,[10] in their study, expressed the feeling that the venous origin of the bleeding had not been sufficiently stressed. They noted that the blood often comes from the not insignificant veins that accompany the middle meningeal artery, or from a tear in a dural sinus. Unfortunately, they did not specify whether the time interval between the trauma and the onset of symptoms differs in the arterial and the venous hemorrhages. Reichert and Morrissey,[12] who were interested in the same subject, pointed out that one should suspect such a lesion when a linear or depressed fracture occurs in close proximity to one of the large dural sinuses. No clinical signs were noted that differentiated these hemorrhages from the arterial variety. Only at operation can the source of bleeding be verified: by inspection, by color of the blood, and by the maneuver suggested by Verbrugghen (compression of the external carotid artery in the neck).

In their discussion of extradural bleeding, Gurdjian and Webster[4] mention that rupture of the middle meningeal artery is a very rare birth injury, but that dural sinus tears are common. Hemorrhages of surgical significance from the latter are unusual, however, because of the low internal pressure. Also the sudden localized trauma that produces dural stripping is absent.

Extradural hemorrhages in the posterior fossa have been reported rarely, the clinical picture being detailed by Coleman and Thomson,[2] Kessel,[8] Guthkelch,[5] and Anderson.[1] These have always been venous in origin, arising from one of the major dural sinuses or the torcular Herophili. The onset of symptoms is slower than in most arterial hemorrhages, but the longest reported interval between trauma and operation is only 15 days (Guthkelch).[5] Some authors have noted that these hemorrhages have followed milder trauma than is usually necessary to produce hematomas over the cerebral hemispheres.

Extradural hematomas are not uncommon lesions in infants, and Ingraham and his associates[6] point out the special problems associated with these small patients, particularly shock due to loss of blood within the hematoma. They also stress the difference in clinical signs, especially the rarity of the initial

loss of consciousness. A local swelling of the scalp at the site of injury is a common finding. Ruptured veins accompanying the middle cerebral artery are the most common source of the bleeding. While the majority of hematomas they reported were venous in origin, the longest latent period encountered in children was seven days after trauma was sustained.

Vance[13] considered that a skull fracture was always present with extradural hemorrhages. However, Roaf,[11] in a more recent series of cases, found this was not always true. In two of the eight patients reported by us, x-rays of the skull failed to demonstrate a fracture.

In reviewing series of cases by various authors, individual cases are often cited where the extradural hemorrhage did not produce sufficient signs and symptoms for more than forty-eight hours after the trauma to warrant operation. This fact has not been emphasized. Gurdjian,[3] in an extensive dissertation on the operative management of traumatic intracranial hemorrhages, reported a patient who sustained an extradural hemorrhage from a ruptured middle meningeal artery whose symptoms were delayed so long that thirty-one days elapsed before operation was undertaken. This stood as a record until Jackson and Speakman[7] described a patient who had sustained a head injury thirty-four days before operation. An encapsulated extradural hematoma was removed from the right frontal area. The source of the bleeding was not determined.

Among our cases of extradural hematomas with delayed onset of symptoms, one was an infant, two were children, and five were young adults. While the trauma was severe enough to produce unconsciousness in only half of these patients, it was sufficient to produce a fracture in six of the eight patients.

The source of bleeding was probably venous in four, and was probably from smaller branches of the middle or posterior meningeal artery in three others. In only one patient was the main trunk of the middle meningeal artery severed. It appears that if the bleeding source is under low tension, the onset of symptoms may be delayed longer than when a sizable artery is torn. In our review of the pertinent literature, we find that the authors have not discussed this point sufficiently to draw definite conclusions.

All our patients survived operation. This is in contrast to the rather high mortality rate in the various series of patients reported, and in our own experience, when operation is undertaken within twenty-four hours of injury. Since many patients have other severe intracranial injuries as well as the extradural bleeding, the mortality is often explainable by the other lesions. The prognosis is much better when the pressure symptoms are slow in developing and the compression of the brain less rapid.

Operation should be undertaken as soon as symptoms suggest the possibility of a hematoma. When intracranial pressure is not promptly relieved, irreparable damage may result, as in Case 3.

When treating a large number of acute head injuries, it is often difficult to separate those with severe injuries from those who will recover without operative treatment. In view of the cases reported here, the inadequacy of observing for only a few hours patients who apparently were not severely injured or who had only a short period of unconsciousness is apparent. It should always be

stressed to the family that the patient should be returned immediately if new symptoms develop, and that people who have sustained head injuries should not be allowed to leave medical observation unaccompanied.

SUMMARY

The case histories of eight patients in whom the onset of symptoms of an extradural hematoma was delayed longer than twenty-four hours after trauma are related. A review of the pertinent literature is summarized and the importance of the venous origin of these hematomas is stressed. When symptoms become manifest, the patient becomes a surgical emergency. Permanent neurological residue and death will result unless the hematoma is promptly evacuated. No deaths resulted in our series of patients, which is in marked contrast to the results obtained when extradural hemorrhages are operated upon within twenty-four hours of injury. The reason for this would appear to be the absence of other severe injuries to the central nervous system which, in themselves, adversely affect recovery after the hematomas are evacuated.

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SURGICAL PROCEDURE FOR LESSENING THE HAZARD OF CAROTID BULB EXCISION

JOHN J. CONLEY, M.D., AND GEORGE T. PACK, M.D., NEW YORK, N. Y.

(From the Surgical Services of Pack Medical Group and St. Vincent's Hospital)

ONE of the serious problems complicating radical surgical procedures of the head and neck has been the grave danger associated with an inadequate supply of blood to the brain. This interference with cerebral circulation occurs most commonly and acutely from an enforced ligation of the internal carotid or both common and external carotid arteries. The gravity of the sudden impairment of blood supply to the brain is considerably increased in individuals over fifty years of age because of coexistent arteriovascular diseases. Ligation or excision of the internal and common carotid arteries as an integral step in the surgical treatment of extensive primary and metastatic neoplasms of the neck has not been adopted because of the serious complications which usually ensue. An alarming operative mortality[1, 2] (sometimes 40 to 60 per cent) may follow surgical treatment for neoplasms of the neck in which ligation or excision of the carotid complex is performed, or, if the patient survives, a hemiplegia may result. In spite of these frightening statistics, a certain number of patients suffering from extensive neoplasms in the neck require excision of the carotid bulb in an attempt to cure or control the disease. The technique of resecting the entire carotid complex (common carotid artery, internal carotid artery, and external carotid artery) was developed for these patients on whom carotid artery surgery is absolutely necessary. We have found by experiments on dogs and trials on human beings that the simple expedient of anastomosing the distal ends of the severed external and internal carotid arteries will permit a continuous flow of blood through this terminal are sufficient to prevent arterial thrombosis, hemiplegia, and death.

RATIONALE FOR IPSILATERAL ANASTOMOSIS OF EXTERNAL AND INTERNAL CAROTID ARTERIES AFTER COMPULSORY OR INTERNAL CAROTID LIGATION OR EXCISION

Vascular transplants of autogenous veins or homologous arteries would solve the problem of maintaining the blood supply to the brain were it not for the frequent handicaps of infection, radiation necrosis and damage, poor tissue bed, and unavailability of suitable grafts. It is well known that the external carotid artery has such large anastomotic communications with other arteries in its terminal distribution that retrograde hemorrhage from its distal severed end can be rapid and great.

In the belief that even a slight flow of blood through the internal carotid artery would prevent the dangerous thrombosis and perhaps preserve the integrity of the brain, it was planned to anastomose the distal severed ends of

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the internal and external carotid arteries on the same side of the neck after excision of the carotid bulb (Figs. 1 and 2). The principle of anastomosing two end arteries, both severed from their proximal and main blood supply, would appear unorthodox, were it not for the known possibility of reversal of blood flow especially from the external carotid artery.

This technique of anastomosing the cut ends of the internal and external carotid arteries high in the neck was developed in the hope of salvaging some patients who would otherwise die of cancer and fatal carotid arterial hemorrhage. This anastomosis permits the blood to flow through the anastomotic

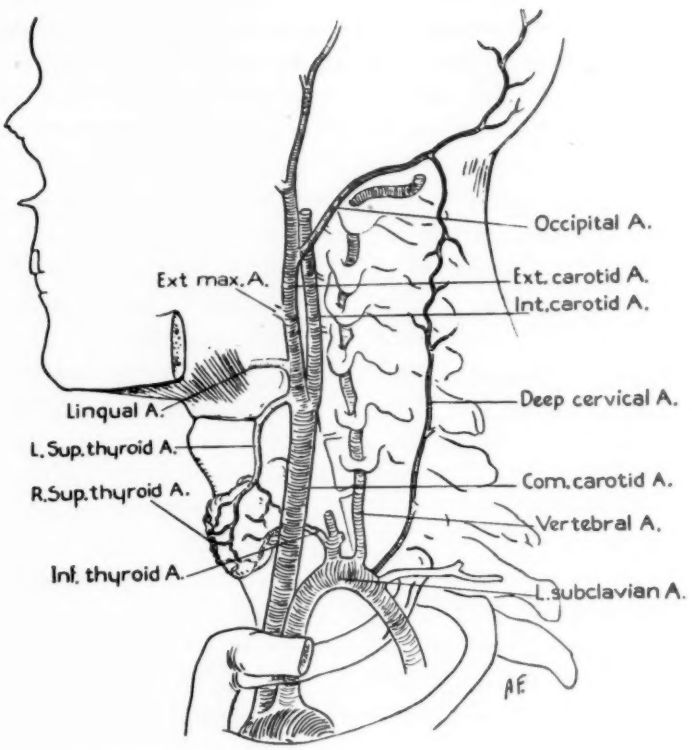

Fig. 1.—Anastomotic network in the neck.

connections of the external carotid artery from the contralateral side into the external carotid artery of the ipsilateral side and thence into the internal carotid artery and circle of Willis in all instances wherein the arterial blood pressure in the ipsilateral internal carotid artery is less than that in the ipsilateral external carotid artery. The blood pressure in the ipsilateral internal carotid artery is not always, or necessarily, lower than that in the corresponding external carotid artery. However, when it is lower, communication with the opposite arterial supply through the anastomotic network of the face and neck may mean the difference between life and death. When the pressure in the ipsilateral internal carotid artery is greater than the pressure in the corresponding external carotid artery, the direction of blood flow after the

anastomosis is completed would be from the brain into the internal carotid and external carotid arteries and thence into the face and neck. This situation would indicate that in such an instance the efficiency of the circle of Willis is more effective than that of the anastomotic bed of the face and neck.

The desirability of having a continuous arterial channel for the flow of blood in either direction, which is accomplished by the anastomosis, is self-evident. The anastomosis has definite advantages over the dead end which exists when the internal carotid artery is ligated. The free movement of blood in itself means additional nourishment to the brain through the medium of the anastomosis. The free movement of arterial blood has another great advantage in that the predisposition to thrombus formation in the artery is markedly diminished. Thrombus formation following ligations of the internal carotid and even common artery have been frequently recorded as a cause of death by the propagation of this thrombus into the middle cerebral artery.

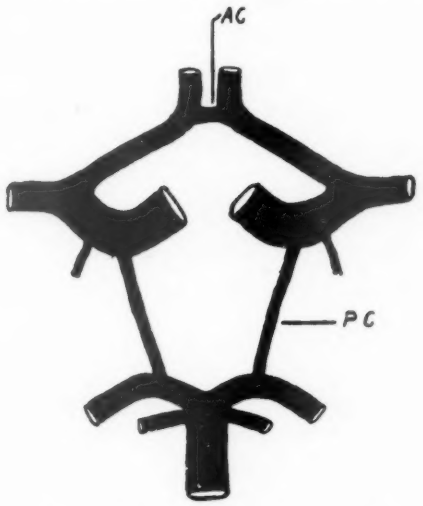

Fig. 2.—Circle of Willis. *AC*, anterior communicating, *PC*, posterior communicating.

INDICATIONS FOR SURGICAL EXCISION OF THE CAROTID BULB

When all the indications for carotid bulb excision are listed, the technique of internal and external carotid artery anastomosis has important applications. These indications are:

1. In postoperative slough of the neck when radical surgery has been utilized following unsuccessful intensive irradiation of the region. The carotid arteries have become exposed and are incorporated in the necrotizing tissues.
2. In postirradiation slough of the neck when the carotid arteries are involved by either the deep extension of residual cancer or the radiation ulceration.
3. In extensive carcinomas of the neck with the cancer invading the walls of the carotid arteries and recognized at operation.
4. In certain carotid body tumors.

5. In certain aneurysms and arteriovenous aneurysms of the carotid bulb of an acquired or congenital nature.
6. In certain cases of trauma to the carotid complex.
7. In certain cases of congenital anomalies of the carotid complex.

There are many instances when it has been necessary to perform radical surgery on the neck after intensive irradiation has failed to cure the cancer. In some instances, the vitality of the skin flaps and deep tissues is so altered by the intensive irradiation and subsequent radical surgery that they necrotize and cause an exposure of the carotid arteries. This is more common when it has been necessary to perform a radical neck dissection, pharyngectomy, and laryngectomy in continuity and with an attempt at primary closure of the pharyngeal and esophageal passages. The danger of sudden and fatal hemorrhage in these cases is always imminent. It may occur through a weakness in the main arterial wall or from any of the cut or ligated branches of the external carotid artery. The time interval may extend from several weeks to three months postoperative.

The artery and surrounding tissue under these circumstances should be freed of their slough with zinc peroxide or Dakin's dressings. The cautious use of streptokinase is helpful. An attempt to cover the exposed artery with a highly nutritious pedicle flap may prove successful. On the other hand, prolonged observation of these particular cases reveals that they usually end in fatal hemorrhage. Ipsilateral anastomosis of the internal and external carotid arteries may prove lifesaving.

Postirradiation slough of the neck, when it is associated with residual cancer or deep irradiation ulceration in the region of the carotid artery, frequently terminates in fatal hemorrhage. If the cancer over the carotid vessels is not controlled by the initial maximum irradiation effort, which it frequently is not, recurrence of the cancer and/or additional irradiation causes a penetrating type of ulceration. Once the pathologic process has involved any of the coats of the carotid artery, further irradiation or conservative surgical measures are of little curative avail. Ipsilateral anastomosis of the internal and external carotid arteries may be helpful.

The neck surgeon is occasionally confronted with a metastatic carcinoma that has invaded the wall of the carotid artery at the time of the initial operation. This is not a common occurrence; however, it may be anticipated in metastatic cancers of the neck that are firmly fixed to the great vessels and deep structures. In the past, it was common practice to remove surgically as much of this carcinoma over the carotid artery as was deemed safe, and to follow this with irradiation of the residual carcinoma in the arterial wall. This usually proved to be fatal eventually. Finally, ulceration appears in the skin and underlying tissue over the diseased area of the carotid artery. As this process advances, the wall of the artery is weakened and most of these patients die of fatal hemorrhage or carotid ligation. Ipsilateral anastomosis of the internal and external carotid arteries may be curvative.

As a result of the high operative mortality in ligation or excision of the internal and common carotid arteries in carotid body tumors,[3] the surgical treatment of this condition has resolved itself into the limited excision of the excessive carotid body tumor tissue associated with the carotid vessels. The tumor, fortunately, is one that does not metastasize and this management, although not final in its curative effect, has been accepted as the only available technique at the present time. These tumors frequently involve the carotid bulb, the vagus and hypoglossal nerves, the sympathetic chain and the internal carotid artery. Their total surgical removal in these instances would include a resection of the bulb and a portion of the internal and external carotid arteries and the three important nerve pathways in most instances. Such a procedure has not been advocated because of the serious complications of excision of the carotid complex in the past, even though the average age of individuals presenting themselves for treatment is in the third decade of life. Anastomosis of the homolateral internal and external carotid arteries or free autogenous vein graft may be utilized in the cure of this tumor.

Aneurysms of the carotid bulb are rare. They may be congenital, posttraumatic, postsurgical, or postirradiation. In some cases, it is possible to repair the vessel without sacrificing the main arterial channel. However, in some instances, it may be necessary to resect the aneurysmal element and repair the defect by a free autogenous vein graft or anastomosis of the ipsilateral internal and external carotid arteries.

TECHNIQUE OF EXTERNAL AND INTERNAL CAROTID ARTERY ANASTOMOSIS

The specific technique of the anastomosis of the internal carotid artery to the external carotid artery is governed somewhat by the local conditions necessitating this procedure. In postoperative slough of the neck following intensive unsuccessful irradiation or in primary postirradiation slough of the neck, the carotid vessels are usually readily accessible from a surgical point of view. It is important to remove all portions of the carotid arteries, the integrity of which have been jeopardized by the irradiation or in the sloughing process so that the anastomosis will have a favorable opportunity for healing. In very extensive cancers of the neck which involve not only the jugular vein but the carotid artery, the dissection is much more involved because of the usual inaccessibility of the arteries for anastomosis and the advisability of removing the entire lateral neck contents, including the great vascular channels, in continuity. This feat is accomplished by the liberation of the entire lateral neck contents through a posterior approach from the margin of the trapezius muscle forward toward the carotid complex. The common carotid artery may be ligated along with the internal jugular vein at the beginning of this procedure. The preparation for ligation of the internal and external carotid arteries should be synchronized with the plans for immediate anastomosis of the stumps of these two vessels. In order to shorten the time elapsing between the excision and anastomosis, the superior limits of the external and internal carotid arteries are liberated and made accessible before the lateral compartments of the neck are removed.

In the case of carotid body tumors, the great vessels are readily accessible and the opportunities for anastomosis are usually not encumbered.

Whenever carotid artery excision or ligation is anticipated, local anesthesia either by infiltration or nerve block is most desirable. Unfortunately, in the surgical approach to extensive cancers of the neck one frequently encounters the cancer invading the arterial wall in an unexpected manner at the time of the major operation, which is usually carried out under general anesthesia.

The operative field should be scrupulously prepared by shaving off all hair and cleansing the skin of the neck, side of the face and upper chest with appropriate antiseptics. Equipment should be available for intra-arterial transfusions, tracheostomy, adequate suction, and inhalation therapy.

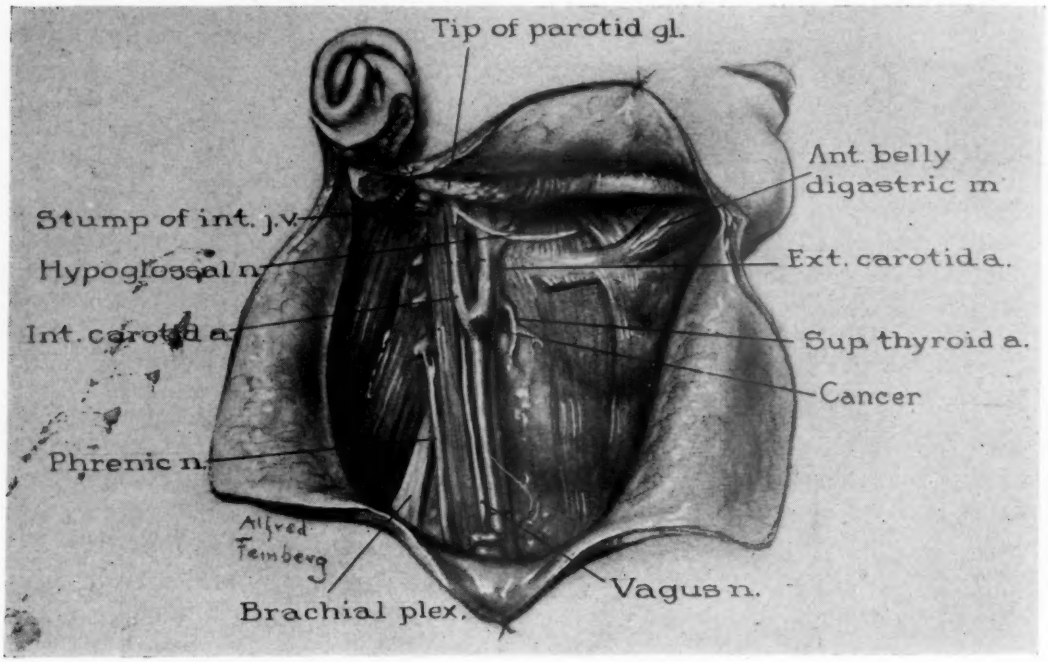

Fig. 3.—Cancer invading carotid bulb.

Whenever possible, intra-arterial pressure tests should be performed upon the various carotid arteries before and after the completion of the ligation and excision. Sweet's[4] sensitive manometer is most satisfactory in securing these readings during the operation. When excision of the carotid bulb is anticipated, the patient should be studied preoperatively by angiography of the circle of Willis in order to ascertain any variations or anomalies in the size of the constituent arteries. Electroencephalograms should be taken before the operation, during the procedure of ligation and anastomosis, in the postoperative period.

The time required for the actual anastomosis is seldom more than five to ten minutes. The superior cervical ganglion is first injected with one per cent procaine to lessen the hazard of cerebral angiospasm. The carotid sinus is

then anesthetized by the injection of one per cent procaine to avoid the carotid sinus syndrome. Appropriate arterial clamps are then placed across the inferior segment of the common carotid artery and other arterial clamps are then placed at appropriate positions on the internal and external carotid arteries. The latter two clamps are placed on the vessels in a vertical position so that when the arteries are cut and the clamps rotated, the most medial aspect of the vessel wall will become accessible for suturing. The vessels are severed about 4 mm. beneath the level of the artery clamps and the anastomosis is then accomplished by interrupted exerting mattress sutures. Only a few of these mattress sutures of 0000 silk on atraumatic needles are necessary to approximate the cut ends of the arteries, depending, of course, on the diameter of the lumens (Figs. 3 and 4). If the diameter of one of the carotid arteries

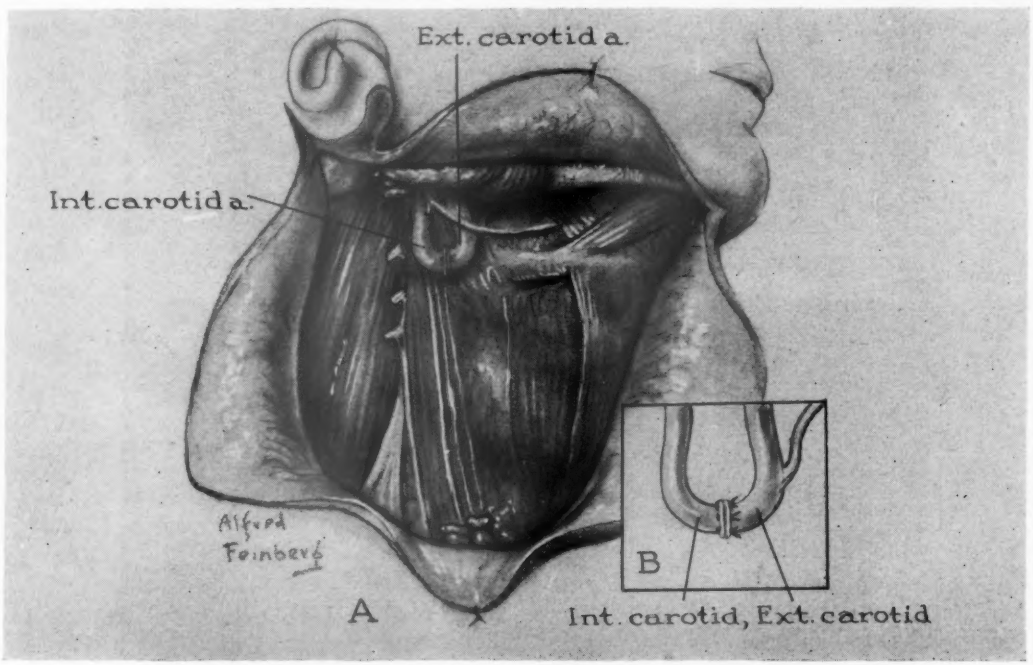

Fig. 4.—*A*, Anastomosis of internal and external carotid arteries. *B*, Detail.

is larger than the other, this disproportion may be overcome by cutting the artery with the small diameter in an oblique manner, thus increasing its overall circumference. As soon as the anastomosis has been completed, the clamps are released and blood will flow through the new arterial junction with considerable pressure. Pulsations are immediately felt in both vessels. There may be a tendency toward acute angulation or kinking at the site of the anastomosis, thus diminishing the effectiveness of the repair. This is overcome by an elevating suture through the wall of the vessel posteriorly and then through the deep muscles of the neck at a higher level, in order to cause a more graceful curvature of the anastomosed vessels. Any tests or measurements of intra-arterial pressures on the cut vessels may be ascertained at this time by appropriate instrumentation. The stump of the common carotid artery is doubly

transfixed with 00 silk and pulled out of its normal position in the neck to the posterior part of the lower neck flap in the region of the trapezius muscle by a through-and-through stitch in the skin. This removes the artery from the line of incision and also from any possibility of contamination by mouth, or by

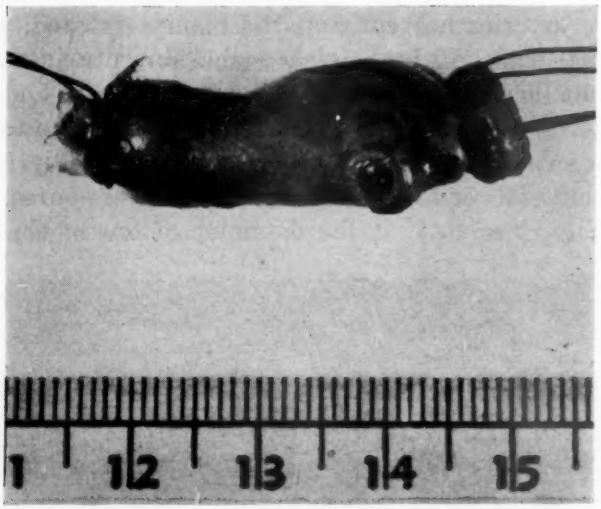

Fig. 5.—Aneurysmal ulceration of carotid bulb (metric scale).

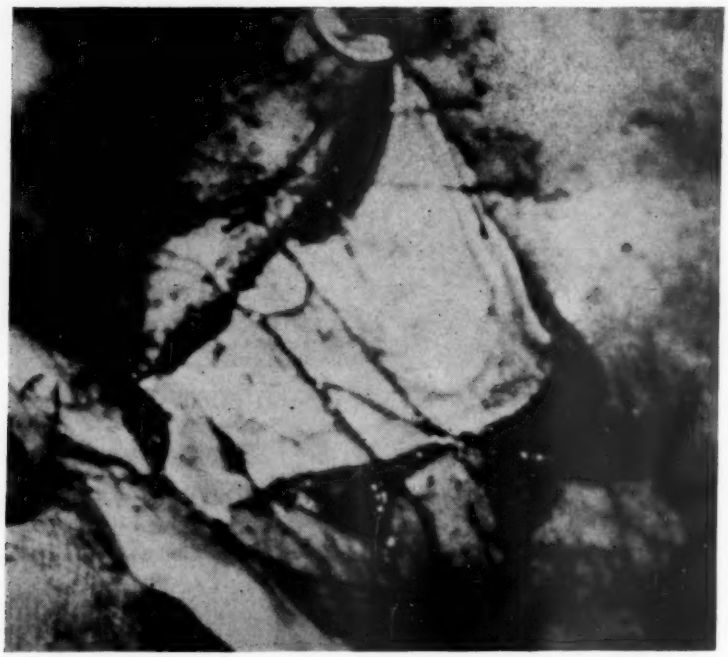

Fig. 6.—Split-skin graft placed over the anastomosis.

pharyngeal or esophageal secretions if a fistula into this region exists or develops. The anastomosis is then covered with the previously prepared skin flaps or in the event that it was necessary to excise the skin, a free graft may be placed over the arteries.

Atheromatous plaques involving the walls of the carotid artery complex are common in the age group over 50 years, in fact atheromatous plaques seem to have a predilection for the region of the carotid bulb. Occasionally, this plaque will extend inferiorly into the common carotid artery and superiorly into the internal carotid artery. If careful palpation and inspection of the arterial wall indicate that a large atheromatous plaque is contained

Fig. 7.—Cancer invading the carotid bulb.

therein, the anastomosis should be accomplished beyond the limits of this condition. If the atheroma extends inferiorly into the common carotid artery, ligation with silk may cause the vessel to rupture with severe hemorrhage. Dandy[5] has recommended that the vessel be ligated with fascia lata or that a cuff of fascia lata be placed about the vessel if ligation with silk or wire is anticipated.

CASE REPORTS

CASE 1.—J. R., a 56-year-old man, began x-ray therapy to the neck in September, 1950, for a squamous-cell carcinoma, grade IV, in the right lateral hypopharynx. This treatment was followed by the implantation of radon seeds. Radiation therapy failed to cure or control the cancer and in March, when the patient was seen by us, residual carcinoma was found in the right lateral hypopharyngeal wall and right pyriform fossa with metastatic cancer in the right deep mid-cervical chain. There was bilateral postirradiation atrophy and fibrosis of the skin and hypopharyngeal mucosa. The patient had had hypertensive heart disease with blood pressure ranging from 160/110 to 190/110 for many years. One year prior to our examination, he had a mild stroke from which he completely recovered. On March 6, a right radical neck dissection in continuity with a radical pharyngectomy, total laryngectomy, and right hemithyroidectomy and upper cervical esophagectomy were performed without any unusual event. Postoperatively the skin flaps about the pharyngostome healed poorly and the common carotid artery and carotid bulb became exposed. Radiation necrosis appeared on these exposed surfaces and an ulceration occurred on the

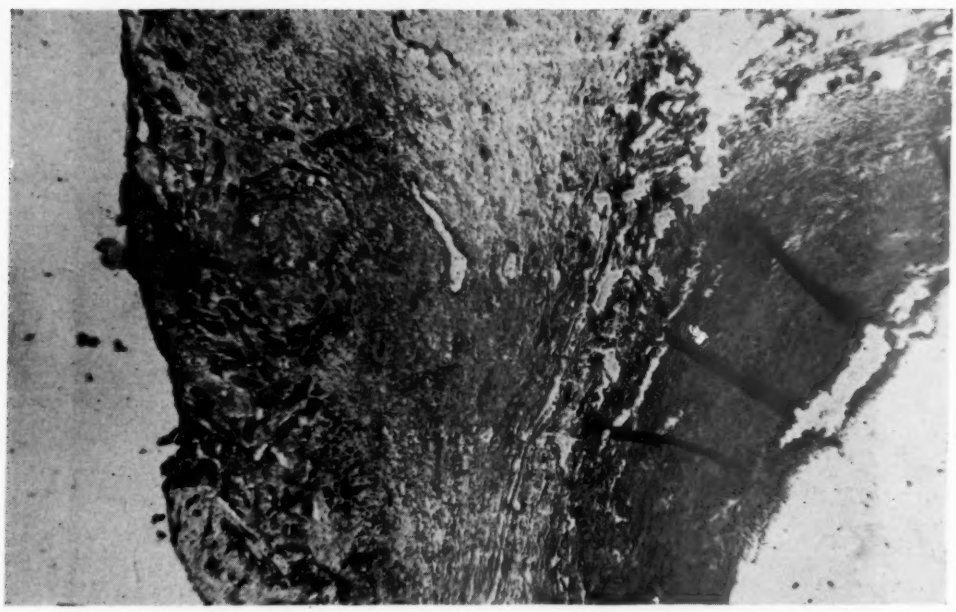

Fig. 8.—Photomicrograph of cancer in adventitia of carotid artery.

anterior aspect of the carotid bulb. This ulceration gradually became greater in diameter and depth. After two weeks of careful observation, it was decided that imminent rupture of this ulcerating aneurysm was about to occur and the patient was scheduled for resection of the common carotid artery, carotid bulb, internal and external carotid arteries. The internal and external carotid arteries were amputated high enough in the neck so that when anastomosed they were well covered by superior neck flaps that had not been in the direct line of irradiation. This patient's blood pressure at the beginning of this first radical operation was 150/80. At the beginning of the second operation for anastomosis, it was 110/80. Shortly after the anastomosis was begun it rose to 160/100. At the end of the operation it had dropped to 135/98. There was a rise in pulse rate from 92 to 110 at the time of anastomosis, but it dropped to 92 at the end of the operation. Respirations at the beginning of the operation for anastomosis were 20; they did not change during the procedure but at the end of the operation had gone up to 28. The patient was heparinized on the first postoperative day and the prothrombin time during the following week varied from 16 to 24. He developed a blood clot under the inferior flap as a result of oozing. This clot was evacuated without any

complication. An electroencephalogram performed on March 30 was interpreted as abnormal with moderate diffuse dysfunction in the frontal lobes. Another electroencephalogram taken on May 15 revealed no change. The patient's postoperative course has been completely uneventful (Fig. 5).

CASE 2.—G. J., a 61-year-old man, underwent a total glossectomy, radical pharyngectomy, laryngectomy, and bilateral suprahypoid dissection on Aug. 23, 1950, for an extremely large, deeply infiltrating anaplastic carcinoma of the tongue which had infiltrated into the pharynx and suprahyoid regions bilaterally. His convalescence from this operation was uneventful. In April, 1951, this patient reappeared with extensive and bilateral metastatic cancer in the

Fig. 9.—Cancer invading the carotid bulb.

deep cervical chains. The mass in the right neck measured 8 cm. in diameter and was necrotic, ulcerating, and bleeding. On April 10, 1951, under general anesthesia, a right radical neck dissection and excision of the common, internal, and external carotid arteries were performed. The cut ends of the internal and external carotid arteries were directly anastomosed by the previously described technique. The ulceration necessitated the removal of a large segment of cervical skin so that a free skin graft had to be used to close the open wound on the side of the neck. This graft was applied directly to the raw surface of the neck and over the

new anastomosis. The lateral pharynx had been opened during the operative procedure and after this was repaired, it also was covered by the free dermal graft. Neurological examination on the evening of the operation was not remarkable. Preoperative electroencephalographic tracings on this patient were normal; on the first postoperative day they were borderline, revealing mild diffuse cerebral dysfunction. On May 3 they were declared abnormal with mild to moderate cerebral dysfunction. The patient was heparinized on the first postoperative day; the prothrombin time varied between 15 and 25. No excessive oozing occurred. This patient's blood pressure at the beginning of the operation was 125/75.

Fig. 10.—Anastomosis of internal and external carotid arteries.

Shortly after the anastomosis it was 160/115 and at the end of the operation was 105/65. The pulse rose from 82 at the beginning of the operation to 90 at the time of the anastomosis and 92 at the end of the operation. Respirations were 20 per minute throughout the entire procedure (Fig. 5).

CASE 3.—J. W., a 63-year-old man, had a grade III squamous carcinoma removed from the lateral aspect of the middle third of the tongue in the fall of 1950. He reappeared in March, 1951, with evidence of metastatic cancer in the left deep mid-cervical lymphatic chain. During a left radical neck dissection in continuity with the floor of the mouth and

tongue on March 21, it was discovered that the cancer had invaded the adventitia of the carotid artery at the level of the carotid bulb. The common carotid artery, carotid bulb, internal and external carotid arteries were excised and the internal and external carotid arteries directly anastomosed. The patient was heparinized on the first postoperative day and the prothrombin times ranged from 16 to 22. There was slight oozing beneath the inferior flap, postoperatively. Electroencephalographic tracings on the second postoperative day were declared normal. The postoperative course was completely uneventful (Figs. 6 and 7).

CASE 4.—S. M., a 71-year-old man, had a laryngectomy performed on Oct. 9, 1950, for a grade II squamous carcinoma involving both ventricular bands and the base of the epiglottis. On April 27, 1951, a right radical neck dissection was performed for a metastatic cancer in a deep, fixed node in the right mid-cervical chain. At the time of this operation, the carcinoma was seen to invade the adventitia of the carotid bulb. The common carotid artery, carotid bulb, internal and external carotid arteries were then excised and a direct anastomosis of the internal to the external carotid artery performed. On the fourth postoperative day an electroencephalographic tracing was interpreted as abnormal, showing mild to moderate dysfunction over the frontoparietal cortex. The patient was heparinized on the first postoperative day and developed a large hematoma underneath the posterior skin flap. This hematoma affected the nutrition of the skin flap and it was necessary to excise a piece of the flap approximately 2 by 4 inches which had become devitalized. A clot was evacuated from the neck, the area was repaired with a large free skin graft applied over the neck wound including the new anastomosis. The skin graft took completely and the patient's postoperative course from that point on was uneventful (Figs. 8 and 9).

One interesting phenomenon in this patient was three intermittent clonic contractions of the left leg on May 8, due to what he described as a pinching of his dressing on the right side of the neck. It was discovered that by irritating the region of the superior cervical ganglion on the right side, clonic contractions in the left leg could be precipitated. Anesthesia of this ganglion prevented any contractions of the left leg upon stimulation or irritation of the ganglion. This demonstrates quite well the delicate balance of blood supply to the brain following excision of the carotid arteries and direct anastomosis of the internal and external carotid arteries. It must be considered that in this patient, who was over 70 years of age, even the slightest amount of cerebral spasm would cause enough ischemia in the region of the right middle cerebral artery to effect clonic contractions of the left leg. This condition disappeared when the free skin graft was placed over the wound.

SUMMARY

A brief review of the pertinent factors concerned with the blood supply to the brain is presented. A new technique of direct anastomosis of the cut ends of the internal carotid and external carotid arteries after excision of the carotid bulb is described. This technique was used successfully without any complications on four patients, all over 50 years of age, on whom compulsory excision of the common carotid artery, internal and external carotid arteries was necessary. The data in their cases are presented. The suggestion is made that the anastomosis of these two terminal arteries permits sufficient circulation of blood gained through collateral external carotid branches and the circle of Willis, to lessen the hazard of cerebral ischemia and thrombosis in the internal carotid artery and branches, with its attendant disablement or death.

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A STUDY OF THE MECHANISMS INVOLVED IN THE PROTECTION AGAINST ULCER FORMATION AFFORDED BY VAGOTOMY IN THE SHAY-PREPARATION RAT

JOHN W. ALEXANDER, M.D., AND K. ALVIN MERENDINO, M.D., SEATTLE, WASH.

(From the Department of Surgery, University of Washington School of Medicine)

INTRODUCTION

SINCE the reintroduction of vagotomy for the treatment of peptic ulcer by Dragstedt and Owens in 1943, vagotomy has been given an extensive experimental and clinical trial by many individuals. There is general agreement that although vagotomy has a number of unwanted side effects in a vast majority of cases, complete vagotomy results in at least a temporary cure and more often a relatively long-lasting cure which is demonstrable both by x-ray and clinical remission of symptoms.[1] There is, however, no complete agreement concerning the mechanism whereby vagotomy protects against, or cures, ulcers.

Dragstedt[2, 23] feels that the corrosive action of the gastric juice is responsible for the production of ulcers and further, that the mechanism of protection provided by vagotomy is the depression of the gastric secretion. Bockus[3] has reported a patient with a long history of medically intractable ulcer treated by vagotomy. Following vagotomy the patient exhibited a free acidity of 90 units, but a markedly depressed motor activity. Yet the ulcer promptly healed, thereby suggesting that the depression of motility may be an important factor in the mechanism of the protection provided by vagotomy. LeVeen[4] demonstrated that the ligation of major gastric arteries results in a depression of gastric secretion. In addition, he showed that this procedure exerts a protective effect against histamine-induced ulcers in dogs. He suggested that vagotomy may be effective because of depressed blood flow.[4] However, Necheles,[5] on the basis of evidence that acetylcholine may constrict gastric end-arteries, has postulated that acetylcholine liberated by vagal stimulation may produce localized areas of anoxia resulting in decreased mucosal resistance thereby allowing digestion of the mucosa by gastric juice. Basically, Necheles feels that vagotomy may be protective because of increased blood flow, an opinion diametrically opposed to that expressed by LeVeen. Moore[6] has stated that since the ulcer cure may outlast the depression of motility and secretion, vagotomy may protect by mechanisms which are as yet unrecognized.

Since the mechanism of protection provided by vagotomy is not completely agreed upon, the purpose of these experiments is to determine if vagotomy protects against the formation of peptic ulcers by the depression of gastric secretion alone or by the combination of other effects of vagotomy such as depressed motility, altered blood flow, or unrecognized effects.

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POSSIBLE MECHANISMS BY WHICH VAGOTOMY MAY PROTECT AGAINST THE FORMATION OF ULCERS

A. *Depression of Gastric Secretion.*—One of the most marked and consistent effects of complete physiologic vagotomy is the depression of gastric secretion. This depression is manifested as a reduction of volume, of acidity, and probably of pepsin.

1. *Volume:* In 57 ulcer cases Grimson[7] demonstrated an average depression of the 12 hour night secretion from 888 c.c. to 340 c.c., a decrease of approximately 60 per cent. Dragstedt,[8] in 135 duodenal ulcer patients, demonstrated a similar average reduction from 1,085 c.c. to 521 c.c., about 52 per cent. Ten patients with gastric ulcer exhibited a 40 per cent reduction. In 7 dogs, Vanzant[9] has demonstrated a depression of volume ranging from 20 per cent to 60 per cent. In 15 rats, Shay[10] has shown a reduction from 96 per cent to 60 per cent.

2. *Acidity:* In 11 duodenal ulcer patients, Grimson[7] demonstrated an average depression of free acidity from 40 units to 0 units, of total acidity from 57 to 25 units, with an elevation of pH from 1.6 to 4.5. Thornton,[11] and Meyer, Rosi, and Stein[12] showed similar reductions. Vanzant[9] has noted, in dogs, that free acidity was usually absent, the total acid curve was low, pH high, usually not less than 3.3 and at times not less than 6.6. With 15 rats, Shay[10] noted a drop in free acidity from 31 to 0 units, of total acidity from 77 to 31 units, with an increase of pH from 1.76 to 3.89.

3. *Pepsin:* The effect of vagotomy on pepsin secretion has not been as widely determined as has the effect on acidity and volume. Moore[6] indicates that, in humans, changes in pepsin are inconstant and negligible. Shay,[10] with 15 rats, reports an average depression from 189 to 107 Mett units.

4. *Significance of depressed gastric secretion as a protective mechanism against ulcer formation:* There is considerable evidence available which indicates a definite relationship between the degree and constancy of gastric acid-pepsin secretion and the incidence of ulcers. However, there is also a significant amount of evidence which indicates that acid-pepsin activity may not be the only important factor in the pathogenesis and perpetuation of ulcer.

The evidence indicating the importance of acid-peptic activity is exemplified by the clinical observation that ulcers are found only where the digestive tract is exposed to gastric juice[16]; that physiologic solutions of HCl administered by continuous drip for 8 hours per day produce ulcers along the lesser curvature[13]; that gastric secretion stimulated by histamine-in-beeswax will produce ulcers in many species[14]; and that surgical procedures which divert the neutralizing influence of bile and pancreatic juice away from the first portion of the small intestine will result in the development of duodenal ulcers.[15]

The evidence which tends to indicate that factors other than acid are significant is adequately expressed by the fact that many normal people without ulcers have high gastric acidity and conversely many ulcer patients have low acidity[16]; further, while it is uncommon, ulcers may exist in the presence of achlorhydria; and acute peptic ulcers heal rapidly even in the presence of

unneutralized gastric contents.[18] Furthermore, the acid-peptic theory does not adequately explain the characteristic location of the ulcer on the lesser curvature nor the periodicity of the lesion.

As an example of the uncertainty which exists over the exact mechanism whereby the depression of gastric secretion might be protective against ulcers, Harkins[17] has pointed out that although vagotomy protects against the formation of ulcers produced by the ligation of the pylorus in rats, the depression of free acid cannot be the entire explanation of the beneficial effects of vagotomy because in individual experiments 7 vagotomized rats all without ulcers had a higher gastric acidity than 10 of the control rats all with ulcers. These authors also point out that depression of volume alone cannot be the entire explanation of the beneficial effects of vagotomy because in the control series 5 rats with a gastric volume of 8 ml. or less presented 126 ulcers, while in the vagotomized series 7 rats with a gastric volume of 8 ml. or more had no ulcers.[17]

Since the importance of total acid-peptic activity in the ulcer diathesis is somewhat controversial, it follows that the degree of protection afforded by vagotomy explained on the basis of depressed gastric secretion also must be controversial.

B. *Depression of Gastric Motility.*—

1. *Effects of vagotomy:* Vagotomy produces a depression of both muscular tonus and of active gastric contractions resulting in an enlarged stomach and prolonged emptying time, and often accompanied clinically by a feeling of fullness, occasional nausea and vomiting, foul eructations, and other symptoms of stasis.

In preoperative x-ray studies by Grimson[7] on 28 patients, none had retention of more than 30 per cent. Preoperatively none had enlarged stomachs nor sluggish peristalsis, while postoperatively 21 had dilated stomachs and all had sluggish peristalsis. In balloon studies, Grimson[7] demonstrated that preoperatively the average height of gastric contractions above resting was 20.5 cm. of water, and as long as one year postoperatively the average height was only 1.6 cm. In rats, Shay[10] observed that postoperatively the esophagus was enlarged 2½ times, the stomach was larger and flabby, the pylorus appeared contracted, and peristalsis was inhibited so that animals could not evacuate food.

2. *Significance of depressed motility:* In ulcer patients hypermotility is the rule.[18] The importance, however, of hypermotility in the pathogenesis and perpetuation of ulcers is difficult to evaluate. Mann and Bollman[13] have shown, with Mann-Williamson dogs, that the ulcer occurs at the bend in the duodenum. This may indicate that the mechanical trauma due to propulsion of gastric contents against the intestinal wall determines the site of the ulcer.[13] Further effects of trauma, which may be enhanced by hypermotility, are demonstrated by the production of ulcers with high cellulose diets in Eck fistula dogs and the healing of these ulcers with bland diets.[19] Bockus[3] has reported a patient who had marked motor depression yet had free acidity of 90 units. In spite of the high acidity his ulcer was healed promptly.

On the basis of the above evidence, it is conceivable that the depression of motility may be an important factor in preventing or curing ulcers, or it may be possible that depressed motility is the essential protective element produced by section of the vagus nerves. As with secretion, the relative importance of motility is unsettled. Therefore, the importance of depressed motility as a protective mechanism of vagotomy also is unsettled.

C. *Other Possible Mechanisms of Protection.*—

1. *Effects of vagotomy on gastric blood supply:* One of the most acceptable statements regarding the pathogenesis of peptic ulcer is that ulcers are caused by the action of gastric juice on an area of decreased mucosal resistance. The unanswered problem of pathogenesis revolves about the mechanism causing a localized, chronic, periodic decrease in resistance of mucosal cells. Necheles,[5] in an attempt to explain all of the facets of the above problem, has postulated that continuous vagal activity produces a constant liberation of acetylcholine which in turn results in a vasoconstriction of gastric end-arteries. The resulting localized areas of anoxia decrease the resistance of mucosa allowing digestion and the production of a chronic ulcer. For this theory to be tenable it must be shown that acetylcholine constricts gastric arteries, a concept which is in opposition to prevailing views.[26] Necheles[5] measured the rate of return blood flow from the stomach of rats and dogs while perfusing them with acetylcholine. In rats there was a decrease of blood flow by 44 per cent; in dogs by 31 per cent to 96 per cent. By perfusing the legs of dogs and rats with acetylcholine, an increased venous return was demonstrated. Therefore, Necheles concluded that while in the periphery acetylcholine may act to produce vasodilatation, in the stomach acetylcholine produces vasoconstriction.[21] Since the stomach is a highly vascular organ, it is likely that anoxia can be produced only in end-arteries. Wherever end-arteries occur one might expect to find ulcers. These areas are the lesser curvature, prepyloric, and upper duodenal.[5, 20] If this proposed theory is correct, vagotomy should be protective by preventing the liberation of acetylcholine by the vagus. In opposition to this view it has been shown that epinephrine, the expected action of which should be opposite to that of acetylcholine, will speed the production of histamine ulcers presumably on the basis of vasoconstriction.[22] Furthermore, LeVeen has stated that vagotomy may protect by causing a decrease in blood flow rather than a localized increase as postulated by Necheles. LeVeen based this conclusion on an experiment which involved ligation of right and left gastroepiploic arteries, section of the vasa brevia and occasionally of the right gastric. He observed that the depression of gastric secretion secondary to the reduced blood supply afforded protection against the formation of ulcers by the injection of histamine-in-beeswax.[4]

Therefore, two opposing viewpoints exist concerning the effect vagotomy has upon gastric blood supply: one proposed by Necheles that vagotomy protects against ulcer formation by increased blood supply to end-arteries, and the other suggested by LeVeen that vagotomy may protect by decreasing gastric blood flow with a secondary depression of gastric secretion.

2. *Unrecognized protective effects:* Moore, who has performed vagotomies primarily on medically intractable chronic cases, points out that in spite of the patient's apparent susceptibility to ulcers, vagotomy produces a clinical cure which outlasts the depression of secretion and motility. Moore has attributed this prolonged protective effect of vagotomy to "some subtle" effect, possibly "a loss of nervous impulses which communicate a patient's adaptive reactions from brain to stomach."[6]

D. *Summary of Possible Protective Effects Produced by Vagotomy.*—

1. Depression of gastric secretion, particularly acid and volume and possibly pepsin.

2. Depression of motor activity with reduction of mechanical trauma and spasm.

3. An effect on blood supply, either to increase blood supply to end-arteries or to decrease blood supply with secondary depression of gastric secretion.

4. Unrecognized effects, possibly failure of environmental situations to affect the stomach by way of the vagi.

As previously indicated there is incomplete agreement as to which of the above mechanisms is of primary importance in the protective effect of vagotomy. However, on the basis of clinical experience and the bulk of experimental evidence, most investigators feel that the depression of gastric secretion is the most likely protective element of vagotomy. The following experiment is designed to determine if vagotomy protects by the depression of gastric secretion alone or if other effects of vagotomy such as depressed motility, altered blood flow, or recognized effects must be evoked also.

METHOD

The rats used in this experiment were divided into two control groups and one experimental group. In the first control group, the objective was to produce ulcers by ligation of the pylorus. In the second control group, in addition to ligation of the pylorus a vagotomy also was done in order to demonstrate the protection provided against the formation of ulcers. In Group III the pylorus was ligated and the vagi sectioned, but, in addition, artificial gastric juice was added to the stomach. If ulcers are not produced, it may be concluded that the depression of gastric secretion is not the mechanism whereby vagotomy protects. If ulcers are produced in numbers equal to those of Group I, it may be concluded that vagotomy protects by the depression of gastric secretion alone and that other effects of vagotomy need not be evoked.

The original procedure of producing ulcers by ligating the pylorus of rats first was reported by Shay[24] in 1945. The protection against the formation of these ulcers by section of vagi was demonstrated by Harkins[17] in 1947.

Technique.—The rats used in this experiment were adult males weighing from 250 to 420 Gm. Previous to any operative procedures the rats were isolated and placed in wire mesh bottomed cages for 48 hours to 60 hours. During this time food was withheld but they were allowed water ad lib. The anesthesia for all operative procedures was Nembutal, 3 mg. per 100 Gm. body weight, intraperitoneally. When subsequent anesthesia was required, as in

Groups IIIa and IIIb, for aspiration of gastric contents or introduction of artificial gastric juice, ether was used. A 3 to 4 cm. incision was made slightly to the left of the midline for the performance of the operative procedure.

In performing the vagotomies, the lobes of the liver were retracted to the right. The esophagus together with the lesser curvature of the stomach was stretched gently by means of traction exerted on the ligatures placed about the pylorus. The vagal fibers were cut as they coursed alongside the esophagus toward the stomach. In many cases, in an effort to do a complete vagotomy, the serosa of the esophagus was incidentally damaged. The artificial gastric juice was added to the stomach by means of a soft rubber No. 10 French catheter used as a stomach tube. The wounds were closed with cotton and covered with a thin coat of 8 per cent celloidin to prevent the animals from contaminating their stomach contents by licking blood and serum. The rats again were isolated in individual wire cages without food or water for 19 to 20½ hours and then sacrificed with 30 mg. of Nembutal intraperitoneally. In removing the stomach for examination, a ligature was placed around the esophagus and the stomach removed. Consequently, the esophagus was not examined. After dipping the stomach in saline to wash off blood and serum a niche was made in the greater curvature and the contents drained into a graduated flask for measurement and later analysis. The stomach then was opened along the greater curvature and pinned out flat. After washing the surface with saline, the stomach was examined for ulcers and fixed in 10 per cent formalin.

The free acid was titrated with 0.1N NaOH to a yellow end point using Töpfer's reagent as an indicator. Phenolphthalein was used as the indicator for total acid with titration to a red end point lasting 30 seconds.

The artificial gastric juice was composed of enough 0.1N HCl to titrate to 75 units of free acid. The choice of this value was made on the basis of Shay's determinations of free acid on the contents of 9 rats' stomachs after 17 to 18 hours. These animals had pylorus ligation and, in addition, had the esophagus ligated in order to prevent contamination.[10] In 99 rats with pylorus ligation, Risley found the average value of free acid was 38 units.[25] These determinations were made on rats without ligation of the esophagus. Therefore, there was contamination of the secretion by hemorrhage and sloughing due to ulcer formation and by swallowed saliva. Risley, in an effort to determine more accurately the acidity of contents not contaminated by ulcer formation, found free acidity 5 hours after pyloric ligation and before ulcers had formed to average 100 units in 23 rats.[25] Since the reported values range from 38 to 100, Shay's value of 77 was chosen as representative of the middle ground. The average value of free acidity from the controls used in this experiment was not utilized because the series is too small. Since the values for pepsin are reported in Mett units by Shay, it is not possible to compute the quantitative amount of pepsin present in a rat's gastric juice; therefore, pepsin of a concentration found in human gastric juice was used, namely, 0.03 per cent.

The formula for artificial gastric juice consisted of 75 c.c. 0.1N HCl, 25 c.c. 0.3N NaCl, and 30 mg. of U.S.P. pepsin 1:3000, to make 100 c.c. of 0.15N solution having a free acidity of 75 units.

Group I, Rats With Pylorus Ligated.—In this group the pylorus was ligated in an attempt to establish this procedure as a method of producing ulcers. Twenty hours postoperatively the rats were sacrificed and the stomachs examined for lesions. In all rats multiple ulcers were found. The lowest total volume secreted after 20 hours was 14 c.c. or 0.31 c.c. per 100 Gm. per hr. The lowest value for free acidity was 69 units. (See Table I.)

TABLE I. PYLORIC LIGATION

RAT NO.	WT. (IN GM.)	NO. OF ULCERS	HR. POST-OPERATIVELY SAMPLE OBTAINED	TOTAL VOLUME	pH	FREE ACID	TOTAL ACID
1	300	5	19	20	1.5	88	124
2	350	40	19.5	25	3.5	0	64
3	220	10	20	14	1.5	80	99
4	280	15	20	18	1.5	75	90
5	300	20	20.5	20	1.5	81	115
6	290	27	19	25	2.0	69	85
7	320	18	19.5	18	2.0	86	100
8	310	10	19	15	1.5	89	110
9	315	16	19	20	1.5	80	105
10	350	14	19.5	21	1.5	90	130
Average	303	17.5	19.5	19.6	1.8	73.8	102.2

Group II, Rats With Pylorus Ligated Plus Vagotomy.—In this group, in addition to ligation of the pylorus, vagotomy was also done. This was an attempt to reaffirm previous observations that vagotomy protects against the formation of ulcers ordinarily produced by tying off the stomach outlet. In all rats vagotomy completely protected against the formation of any ulcers (Table II). In none of the rats of Group II of this experiment was free acidity present nor did the total volume exceed 7 c.c. or 0.13 c.c. per 100 Gm. per hr.

TABLE II. PYLORIC LIGATION PLUS VAGOTOMY

RAT NO.	WT. (IN GM.)	NO. OF ULCERS	HR. POST-OPERATIVELY SAMPLE OBTAINED	TOTAL VOLUME	pH	FREE ACID	TOTAL ACID
11	300	0	20	4.5	4	0	82
12	320	0	19.5	4.5	6	0	30
13	250	0	19.5	6.5	5	0	55
14	260	0	20	4.5	5	0	80
15	290	0	19	6	6	0	40
16	350	0	19.5	5	4	0	35
17	290	0	20	5	5	0	60
18	310	0	20	4.5	5	0	44
19	315	0	19.5	6	6	0	51
20	300	0	19.5	7	6.5	0	63
Average	298.5	0	19.6	5.4	5.4	0	54

Group IIIa, Ligation of the Pylorus, Plus Vagotomy, Plus the Addition of Artificial Gastric Juice.—In this group, an attempt was made to evaluate the effect on ulcer formation of the addition of artificial gastric juice to the rat's stomach following vagotomy and ligation of the pylorus. Artificial gastric juice was added, aspirated after 3 hours, and replaced with fresh gastric juice.

This was repeated 4 times during the next 20 hours. The volume added was that amount of artificial juice plus the anticipated secretion from the vagotomized stomach which would not exceed the total volume secreted over a similar period by the control rats of Group I. In this group multiple ulcers were present in all rats.

Group IIIb.—This group represents a control group which was subjected to exactly the same procedure as Group IIIa except that isotonic saline was used rather than artificial gastric juice. This was done in order to rule out the possibility that ulcers might be produced by elevation of hydrostatic pressure, trauma incident to intubation, additional anesthesia, etc. In this group no ulcers were present.

The results for Group IIIa and IIIb are reported in detail. (See Tables IIIa and IIIb.)

TABLE IIIa. PYLORIC LIGATION AND VAGOTOMY PLUS INTRAGASTRIC ARTIFICAL GASTRIC JUICE

RAT NO.	WT. (IN GM.)	NO. OF ULCERS	ANALYSIS OF ASPIRATED VOLUMES* AVERAGE VOLUME	AVERAGE pH	AVERAGE FREE ACID	AVERAGE TOTAL ACID
28	300	5	11.0	2.6	36.0	52.0
29	310	14†	9.5	3.0	37.0	48.5
30	260	14†	8.7	2.1	38.5	47.0
31	310	18	9.1	2.6	33.6	41.6
32	300	22	10.6	1.9	36.8	52.4
33	290	19	9.9	1.8	59.0	50.8
34	310	16†	88.1	1.8	39.7	47.2
35	330	19	10.8	1.9	40.2	51.6
36	310	13†	9.7	2.1	33.5	50.5
37	340	14	9.8	2.1	36.2	47.8
Average	315	15.4	9.2	2.2	39.0	49.0

*Analyses were done on 5 aspirated specimens for each rat, 3, 6, 9, 17, and 20 hours postoperatively. Ten c.c. of artificial gastric juice were added after each aspiration. (See text.)

†Perforated ulcer present. All perforations occurred immediately before the twentieth hour. Therefore, the average figures for these individual animals have been computed on the basis of 4 aspirated specimens rather than 5.

TABLE IIIb. PYLORIC LIGATION AND VAGOTOMY PLUS INTRAGASTRIC SALINE

RAT NO.	WT. (IN GM.)	NO. OF ULCERS	ANALYSIS OF ASPIRATED VOLUMES* AVERAGE VOLUME	AVERAGE pH	AVERAGE FREE ACID	AVERAGE TOTAL ACID
38	330	0	9.9	–	0	11.0
39	360	0	10.0	–	0	10.5
40	260	0	9.0	–	0	9.6
41	310	0	10.0	–	0	10.0
Average	315	0	9.8	–	0	10.2

*Analyses done on 5 aspirated specimens for each rat at 3, 6, 9, 17, and 20 hours postoperatively. Ten c.c. of saline were added after each aspiration. (See text.)

DISCUSSION

In Group I ligation of the pylorus produced multiple gastric ulcers. In a series of 99 rats, Risley, after ligating the pylorus, found multiple ulcers present in all 99 after 16 hours, thereby establishing this procedure as a reliable experimental method for the production of acute ulcers.[25] In Group II after ligation of the pylorus, vagotomy protected against ulcers. In 1947, Harkins,

with 20 rats, demonstrated that vagotomy protected against ulcer in all cases; whereas with 22 control rats, ligation of the pylorus produced an average of 22 ulcers per rat.[17] In Group IIIa all the effects of vagotomy were present with the single exception of depressed gastric secretion. Since multiple ulcers were produced, it may be concluded that depression of gastric secretion is a major protective mechanism of vagotomy.

Since the stomachs of the rats in Group IIIa had a depressed motor activity, it may also be concluded that this factor is not a major protective element of vagotomy in rats. However, until it can be shown that the number and character of ulcers present in Group IIIa, as well as the character of the gastric contents, are comparable to Group I, it cannot be said that depression of motility is completely without a protective effect. A consideration of these factors is included later in the discussion.

In rats of Group IIIa, since acetylcholine is no longer being liberated by vagal stimulation, there can no longer be a constriction of gastric end-arteries as proposed by Necheles. This assumed absence of vasoconstriction is inadequate to protect against the formation of ulcers. Therefore, Necheles' vascular theory of ulcer production as outlined previously does not seem to be a significant protective factor of vagotomy in rats.

No conclusions can be drawn concerning the suggestion advanced by LeVeen that vagotomy may protect by depression of blood flow with secondary depression of gastric secretion, except those which have been discussed previously concerning the effects of depressed gastric secretion.

In order to conclude that depression of gastric secretion is the *only* protective factor, a more detailed comparison of Groups I and IIIa is necessary.

A. *Comparison of Number and Character of Ulcers.*—In both groups a large number of pin-point defects of the mucosa were present. In recording the number of ulcers, these were ignored and only those ulcers larger than 1 mm. were tabulated.

A comparison of the average number of ulcers for each group indicates that Group I has a higher index of ulceration; however, a comparison of individual rats tends to show that in a large series it would not be unlikely that the average for each group might be similar. If such were the case, it would tend to indicate that the depression of gastric secretion is the only protective mechanism of vagotomy.

B. *Comparison of Gastric Contents.*—

1. *Volume:* Five hours after ligation of the pylorus, Risley found the average volume in 23 rats to be 6.3 c.c. or, expressed as rate of secretion, about 1 c.c. per 100 Gm. per hr. The rate of secretion was not considered in doing the experiment reported here; the volume total only was controlled. This may represent a valid criticism of the technique employed. For example, in rats of Group IIIa, 5 c.c. of artificial gastric juice were immediately added to the rats' stomachs after ligation of the pylorus, whereas in Group I, at a secretory rate of 1 c.c. per 100 Gm. per hr., almost 2 hours would be required to reach this volume. Furthermore, at 3 hours in Group IIIa, a total of 10 c.c. of artificial gastric juice was added, a value which would not be reached until

about 3½ hours after ligation of the pylorus. The obvious effect of the experimental procedure is a somewhat more prolonged exposure to a greater volume of gastric juice in Group IIIa than in Group I. Even though the discrepancy is not great this would theoretically result in a greater degree of ulceration in Group IIIa than in Group I.

2. *Acidity:* It may be noted that free acidity in Group I averaged about 73 units whereas an interpolated average for Group IIIa was about 40 units. Although the artificial gastric juice utilized had a free acidity of 75 units, a portion of this was neutralized by mucosa, saliva, etc., until 3 hours after being introduced free acidity average about 45 units. Consequently, the rats of Group IIIa were exposed to gastric juice which had a lower free acidity than those of Group I and might possibly have been expected to have a lesser degree of ulceration and to partially balance the error produced by the difference in volume which was noted previously.

C. *A Comparison of Weight, Sex, and Age of Group I and Group IIIa.*— The weight and sex of the two groups compare well; however, no data are available concerning differences in age. According to Risley these factors are important since the younger the rat, the more easily ulcers are produced. For the most consistent results, ulcers are best produced in male, litter mate rats of about 2 to 3 months of age. Because of the above discrepancies, it cannot be definitely stated that depression of gastric secretion is the *only* protective mechanism of vagotomy in rats; however, on the basis of data available it does not seem too unlikely that such might be the case.

CONCLUSIONS

1. The development of peptic ulcers in the Shay-preparation (pylorus-ligated) rat has been reproduced. The validity of vagotomy as a means of protecting the pylorus-ligated rat against the production of ulcer has been reaffirmed.

2. In rats with pylorus ligation protected by vagotomy, the introduction into the stomach of artificial gastric juice regularly produced peptic ulcers. The artificial gastric juice consisted of acid and pepsin in amounts usually found in these animals and was periodically instilled into the stomach to conform approximately with the normal rate of secretion.

3. The character of the ulcers in the latter group was similar in all respects to those observed in pylorus-ligated rats. The number of ulcers per stomach was similar in the two groups but not identical.

4. The depression of gastric secretion is the major mechanism whereby vagotomy protects against the formation of ulcers produced by ligation of the pylorus in rats. Other factors have been discussed but do not appear to be of importance.

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TRANSFUSION OF HEMOLYZED BLOOD

WORTHINGTON G. SCHENK, JR., M.D., CHARLES E. WILES, JR., M.D., AND JOHN LINDENBERG, M.D., BUFFALO, N. Y.

(From the Department of Surgery, Edward J. Meyer Memorial Hospital, and the University of Buffalo Medical School)

BEFORE the advent of the current methods for drawing, storing, and transfusing whole blood, it was frequently noted that the crudely handled blood was hemolyzed to varying degrees prior to transfusion. Many times the clinician was forced to make the choice as to whether he should administer this partially hemolyzed blood to a desperately ill patient or give none at all. The former choice was made most often with surprisingly good results; reactions, hemoglobinuria, and evidence of renal damage being relatively rare. Because of these observations, experimental work in the dog was initiated in an attempt to quantitate the effects of massive transfusions of hemolyzed whole blood.

METHOD

Normal, adult, mongrel dogs were carefully studied before transfusion with detailed hematologic and urinary determinations. Each dog's blood volume was determined by the T-1824 dye method and from 10 per cent to 20 per cent of the dog's blood volume removed rapidly from a femoral vein without anesthesia. This blood was drawn into a vacuum bottle containing the standard citric acid-sodium citrate-dextrose preservative solution and was immediately frozen in a dry ice-alcohol bath at –70° C. This produced essentially complete hemolysis. This unfiltered solution was then immediately returned by slow intravenous drip to the same animal from which it had been drawn to obviate any cross-matching problems. The animal's blood and urine were then studied carefully for several weeks in an attempt to determine the fate of the transfused material.

CLINICAL OBSERVATIONS

The clinical changes observed on transfusion are tabulated in Table I. Of the seven transfusions only one produced any reaction and there is good reason to believe this could have been avoided. In this transfusion, the first listed in the table, the blood was given very rapidly through large syringes. When the same animal had twice the volume of blood administered two weeks later by slow drip, no reaction could be detected. All the blood was administered by slow intravenous drip thereafter.

All animals had a normal rectal temperature at the conclusion of the transfusion.

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HEMATOLOGIC OBSERVATIONS

Red blood cell counts, hemoglobin determinations, and hematocrit readings showed some irregular variations but in general they merely reflected the findings of the total red blood cell mass determinations and therefore only the latter are presented. It was found that the total red cell mass was reduced by almost the exact amount the dog was bled and the other determinations mentioned showed corresponding depression. All determinations showed slow rise and reached the pretransfusion levels in about two and one-half weeks.

TABLE I. CLINICAL REACTIONS TO MASSIVE TRANSFUSIONS OF HEMOLYZED WHOLE BLOOD

DOG NO.	CLINICAL REACTION	% BLOOD VOLUME HEMOLYZED
89*	Retching, urination, defecation, convulsions, coma; recovery	10
91	None	10
89	None	20
130	None	20
127	None	20
125	None	20
162	None	20

*This transfusion was given very rapidly through large syringes; all subsequent transfusions given by slow drip.

The rate of erythrocyte regeneration in controls following hemorrhage with no replacement is compared in Table II with the rate in animals which were bled and then had the withdrawn blood hemolyzed and reinfused. It is evident that the rate of regeneration is remarkably constant regardless of the amount of blood withdrawn and uninfluenced by the hemolyzed blood transfusion. It was concluded that the transfusion of hemolyzed blood to an anemic dog neither helped nor hindered the return to a normal hematologic picture.

TABLE II. RATE OF ERYTHROCYTE REGENERATION IN CONTROL DOGS FOLLOWING HEMORRHAGE AND IN DOGS HAVING BLOOD REMOVED, HEMOLYZED, AND REINFUSED

DOG NO.	% BLOOD VOLUME REMOVED	R.B.C. FORMED PER DAY (IN C.C.)
Controls (blood removed and discarded)		
127	30	12.4
94	30	12.7
After Transfusion of Hemolyzed Blood (blood removed, hemolyzed, and reinfused)		
91	10	12.8
89	20	11.8
130	20	12.8

BLOOD CHEMISTRY

The highest serum nonprotein nitrogen for the six dogs on which the study was made is shown in Table III along with the posttransfusion day on which it occurred. Only the last two listed exceeded the upper limit of normal for this laboratory and these only by small amounts. Certainly marked nitrogen retention does not result. In two cases the serum NPN dropped initially presumably due to hemodilution.

These observations concur with those of Parsonnet and associates,[1] who found that hemoglobinuric nephrosis could not be produced in dogs in a state of hemorrhagic shock by infusions of hemolyzed whole blood or hemoglobin

solutions. Although the metabolic fate of the transfused material rather than the development of renal lesions was the aim of this study, three animals have been sacrificed at one, three, and five months posttransfusion and no gross lesions were evident in any kidney nor any microscopic lesion in the two sectioned.

TABLE III. MAXIMUM SERUM NONPROTEIN NITROGEN DETERMINATIONS AFTER MASSIVE TRANSFUSION OF HEMOLYZED WHOLE BLOOD

DOG NO.	HIGHEST POSTTRANSFUSION NPN	DAY ON WHICH MAXIMUM NPN OCCURRED
130	23.0	2
162	26.4	1
127	28.6	1
125	28.7	8
91	37.5	9
89	43.0	2

URINARY FINDINGS

Within seven minutes after the transfusion was begun the urine turned bright red, later changing to mahogany or even black and remaining thus for about thirty-six hours after which it cleared very rapidly. The pigment was primarily hemoglobin. In order to be able to evaluate quantitatively the significance of the nitrogenous products appearing in the urine, precise nitrogen balance studies were carried out on two animals. These animals were maintained in exact equilibrium or slightly positive balance in the fore-period by nutritionally complete gavage feedings. Perineal urethrostomies were performed to permit easy catheterization four times in each twenty-four hour period to obtain all urine without any possibility of contamination.

The nitrogen balance curves of these two animals are shown in Fig. 1. The abrupt shift of the balance from positive or equilibrium to negative is evident. The detailed breakdown of the fate of the transfused nitrogenous material is given in Table IV. From these figures it is apparent that this is a very poor method for administering nitrogen since 65 per cent of the total amount administered is thrown away very rapidly, mostly as protein and hence probably not even metabolized before being discarded. Of the 35 per cent retained, plasma protein present in the hemolyzed blood could account for four-fifths if it were all retained indicating the probability that only 20 per cent of the nitrogenous material administered as hemoglobin or other cellular constituents was retained.

TABLE IV. THE METABOLIC FATE OF THE NITROGENOUS COMPONENTS AFTER TRANSFUSION OF HEMOLYZED WHOLE BLOOD

	NITROGEN IN GRAMS	
	DOG 125	DOG 162
Nitrogen Administered		
Total nitrogen given as hemolyzed blood	9.1	10.3
Nitrogen in hemolyzed blood present as plasma protein	1.9	1.9
Nitrogen Loss in Excess of Basal		
Total urinary nitrogen loss posttransfusion	34	6.6
Protein nitrogen loss of posttransfusion	6.0	6.0
Per cent of total nitrogen given which was retained	5.5	36

TRANSFUSION OF HEMOGLOBIN SOLUTIONS

A good deal of work has been done on the possible use of hemoglobin solutions as blood substitutes[4-7] but most of the studies deal principally with the question of whether or not renal damage is produced by the solutions[3, 5] rather than the question of utilization of the nitrogenous products given in the hemo-

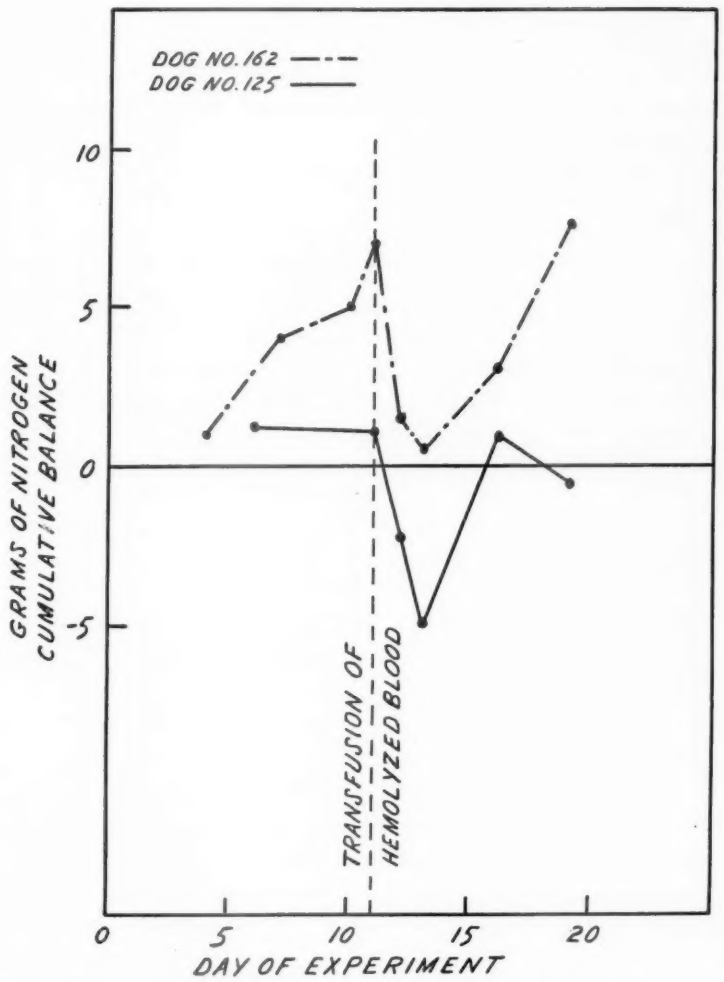

Fig. 1.—Cumulative nitrogen balance of dogs before and after transfusion of hemolyzed whole blood.

globin solutions. It is with this latter question that we have concerned ourselves, primarily. The fate of the nitrogenous products of small hemoglobin transfusions was studied by Pommerenke and associates,[2] but in that work the amounts used were so small that the renal threshold for hemoglobin was not exceeded and the method is hardly comparable to our massive transfusions.

METHOD

Two healthy, adult, female mongrel dogs were placed on a nitrogen-free regimen as described by Pommerenke and associates[2] with the modification that

the dogs were fed 300 c.c. of 50 per cent sucrose daily by gavage, supplying 600 calories. Water was available in the cages at all times. The lack of diarrhea as a problem was a pleasant surprise.

On the sixth day of the nitrogen fast 20 per cent of the dogs' blood volume was removed using the same technique as with the hemolyzed blood experiments. Hemoglobin solutions free of plasma protein and cellular residues were prepared from this blood,[2] and sufficient dextrose was added to the solutions to insure their isotonicity. These solutions were immediately returned to the animals from which they had been taken by slow intravenous drip infusion. The fate of the nitrogenous material so administered was evaluated by careful quantitative urine study.

There were no reactions or febrile responses noted.

URINARY FINDINGS

The urine became bright red within ten minutes after the infusion was begun. It turned dark red in a few hours, slowly cleared, and appeared normal in forty-eight hours.

There was a marked increase in urinary volume noted in the twenty-four to forty-eight hours posttransfusion. In one animal the volume doubled and in the other it tripled from its basal value.

Phenolsulfonphthalein excretion tests were normal at the conclusion of the experiment.

TABLE V. PERCENTAGE OF ADMINISTERED NITROGEN APPEARING IN THE URINE FOLLOWING TRANSFUSION OF HEMOGLOBIN SOLUTIONS*

DOG NO.	FIRST 3 DAY PERIOD POSTTRANSFUSION	SECOND 3 DAY PERIOD POSTTRANSFUSION	TOTAL
102	75	20	95
138	62	25	87

*Dog's own blood free of plasma protein and cell rests.

NITROGEN METABOLISM

The influence of these transfusions on the animals' nitrogen metabolism is seen in Fig. 2. The percentage of the administered nitrogen given as hemo globin solution which appeared in the urine in excess of the basal nitrogen output is seen in Table V.

From these data it is concluded that the nitrogenous material of transfused hemoglobin solutions does not contribute to the nitrogen economy of the recipient but is rapidly and almost completely thrown away in the urine.

IRON METABOLISM

An attempt was made to determine the fate of the iron present in hemolyzed blood and hemoglobin solutions after transfusion.

After careful cross-matching, four dogs were bled 20 per cent of their blood volumes rapidly without anesthesia. Two of these dogs then had an immediate replacement transfusion of an equal quantity of hemolyzed blood from a compatible Fe^{59} tagged donor. The other two had an immediate replacement transfusion of an equal quantity of hemoglobin solution prepared from Fe^{59} tagged donors. Knowing the total activity administered to each animal as radio-iron,

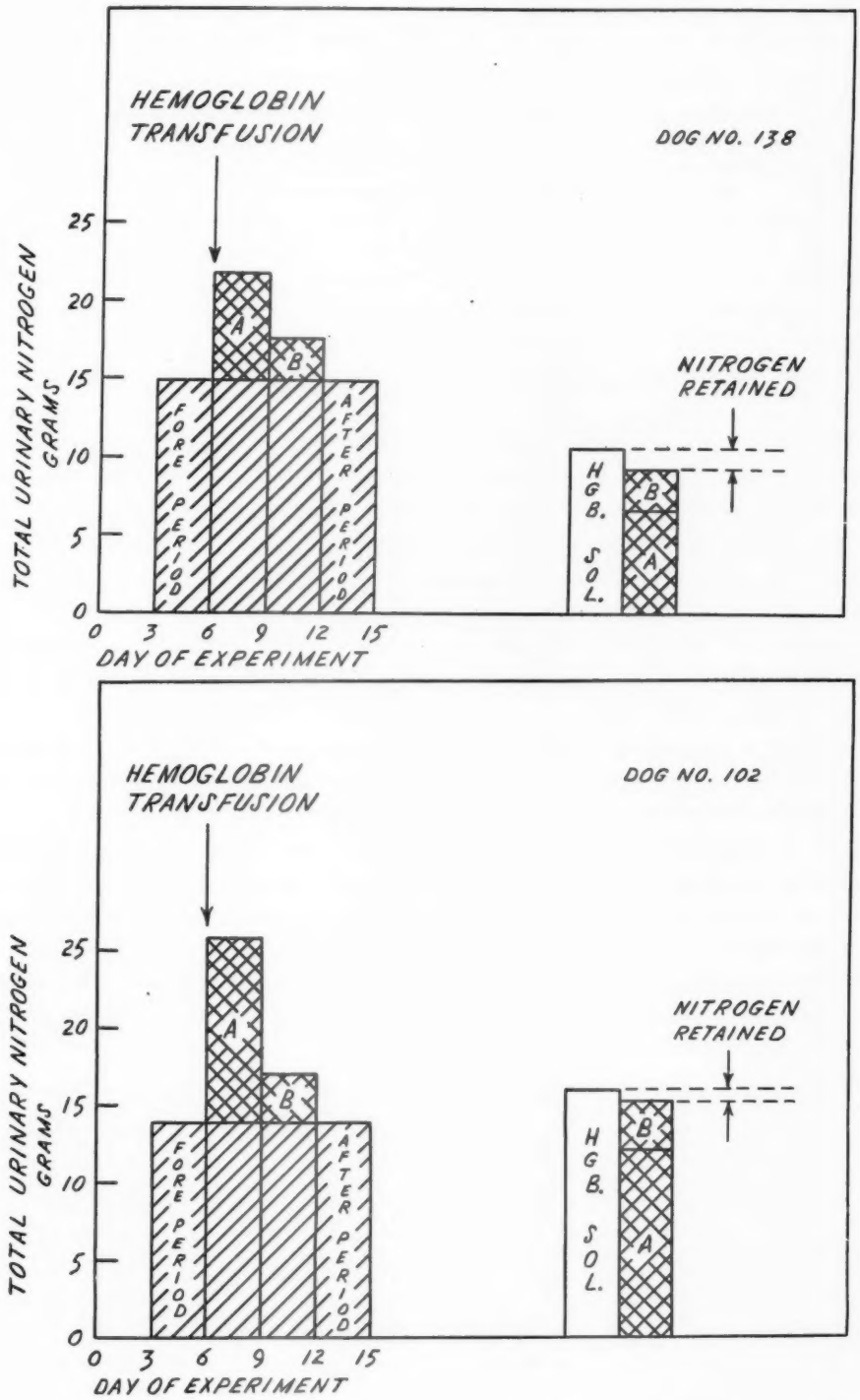

Fig. 2.—*Left,* Urinary nitrogen output of nitrogen fasting dogs before and after transfusion of hemoglobin solutions. *Right,* Comparison between nitrogen administered as hemoglobin solution and nitrogen appearing in urine in excess of basal output.

the proportion of the iron which was retained during the first three days post-transfusion was determined and is shown in Table VI. These few observations do not warrant any conclusions other than to lend the impression that in the case of the hemolyzed whole blood the percentage of iron retained closely approximates that of nitrogen while in the case of the hemoglobin solutions considerably more iron was retained than nitrogen.

TABLE VI. PERCENTAGE OF ADMINISTERED IRON RETAINED AFTER TRANSFUSION OF HEMOLYZED BLOOD AND HEMOGLOBIN SOLUTIONS

DOG NO.	% Fe^{59} RETAINED IN FIRST 3 DAYS POSTTRANSFUSION	ADMINISTERED AS
181	36	Hemolyzed blood
180	Unsatisfactory—blood not completely hemolyzed	Hemolyzed blood
197	70	Hemoglobin sol.
199	80	Hemoglobin sol.

SUMMARY AND CONCLUSIONS

1. Massive quantities of hemolyzed whole blood and hemoglobin solutions can be administered to the dog without clinically detectable ill effects.

2. The transfusion of hemolyzed whole blood to an anemic recipient has no influence on the rate of blood regeneration or re-establishment of a normal hematologic picture.

3. Retention of nonprotein nitrogenous material in the plasma as evidence of renal insufficiency does not occur following the transfusion of massive quantities of hemolyzed whole blood.

4. Most of the nitrogenous material given in the hemolyzed blood or hemoglobin solution is rapidly discarded in the urine without contributing to the animal's nitrogen economy.

5. There is suggestive evidence that more of the iron present in hemoglobin solutions is retained than nitrogen after transfusion but that the amounts of iron and of nitrogen retained after hemolyzed whole blood transfusion are approximately equal.

6. The appearance of slight to moderate amounts of hemolysis in the serum of blood stored for human transfusion is probably not a contraindication to the use of that blood.

The authors wish to express their appreciation for the technical assistance of Miss Sarah Camiolo and Mrs. Elva Wilkins.

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ANATOMIC CHANGES PRODUCED BY NOVOCAIN AND PHENOL INFILTRATION IN THE SYMPATHETIC GANGLIA

N. Rabinovici, M.D.,* Jerusalem, Israel

THE efferent sympathetic pathways to an extremity or to the abdominal viscera are blocked temporarily by a paravertebral block as effectively as by operative excision. The sympathetic nerves may be blocked by the injection of Novocain (Mandl[12]) or alcohol (Swetlow,[20] White[21]) directly into the sympathetic ganglia, or by the infiltration of the loose connective tissue surrounding the ganglia.

When used as a local anesthetic, Novocain blocks the conduction of nerve impulses and depresses the sensitivity of the somatic and sensory nerve terminations. The anesthetic is believed to interfere with the ability of the axone to become depolarized (Bennet[18]), or to induce decreased permeability of the lipoid layer covering the nerve. Leriche[11] believes that Novocain blocks the painful reflexes induced by trauma or vascular diseases and restores the neurovegetative equilibrium.

Little has hitherto been published on the anatomic changes induced by the injection of Novocain into the sympathetic ganglia. So far the only attempt to study the effects of intragangliar infiltration was made by Merrick,[14] using alcohol.

A solution of 6 per cent phenol in water is considered by Mandl[13] and by Pitkin[18] to have a selectively destructive affinity for sympathetic fibers, and is sometimes used for chemical sympathectomy or even for local anesthesia,[16] although its mode of action is not definitely known.

In the present study we present data on the changes produced by infiltration with 1 per cent Novocain or 6 per cent phenol on the sympathetic ganglia in cats.

TECHNIQUE AND MATERIALS

Twenty-one cats of varying sizes and weights were used in this investigation. Ether and Pentothal Sodium, 70 mg. per kilogram of animal weight, administered intravenously, were used as anesthetics. A laterocervical incision at the level of, and posterior to, the mastoid was made. The muscles were transfixed and the carotid artery and the vagus nerve located. In the cervical region the sympathetic trunk was intimately connected with the vagus nerve and ran parallel and medial to it. The superior cervical ganglion was situated immediately above the ganglion nodosum of the vagus nerve in a posterior and medial position. As soon as it was located the superior cervical ganglion was infiltrated with 0.3 c.c. of 1 per cent solution of Novocain. In a similar operation performed on the other side, the superior cervical ganglion was infiltrated with 0.3 c.c.

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*From the Surgical Department, B, Hadassah University Hospital.

of a 6 per cent aqueous solution of phenol. In five other animals serving as controls the cervical ganglia were infiltrated with the same amount of normal saline solution. The incision was sutured and a sterile dressing was applied.

The animals were killed with ether and both of the superior cervical ganglia were extirpated 24 hours, and 3, 7, 14, 21, 30, 45, 60, 75, and 90 days following gangliar infiltration. One half of each ganglion was fixed in 96 per cent alcohol and the second half in 4 per cent formalin. Histologic sections were prepared from each segment and stained with erythrosin toluidine blue and the Bielschowsky silver impregnation method.

Fig. 1.—Normal sympathetic cervical ganglion. Bielschowsky's silver impregnation (×370).

RESULTS

The Claude-Bernard-Horner syndrome regularly appeared after infiltration of the superior cervical ganglion. It was more pronounced on the side infiltrated with phenol where apparent enophthalmus due to lid lag and marked myosis appeared after an average of half an hour and disappeared between the tenth and the seventeenth days. On the side injected with Novocain the syndrome was less conspicuous, appearing between 3 and 24 hours after injection, and usually disappearing after 3 days. No changes were observed in the animals infiltrated with saline solution.

Gross Appearance of the Sympathetic Ganglia After Infiltration.—There were no differences in the gross appearance of the ganglia infiltrated either with Novocain or with phenol. The periganglionic capsule of ganglia excised 24 hours after infiltration were found to be congested with multiple hemorrhagic points over the entire surface while the ganglia excised 3 days after infiltration seemed to show an acute inflammatory process involving the whole surface of the ganglion. The surrounding connective tissue was also inflamed, forming a block in which the ganglia were embedded. On transverse section the peripheral part of the ganglia seemed to be congested while the central part was softer

in consistency and yellowish in color. At 7 days the surface of the periganglionic capsule was irregular and congested and adhered firmly to the ganglion nodosum of the vagus. On section it appeared yellow, soft, and necrotic. At 14 days the adhesions surrounding the ganglia were marked, and at 21 days formed a dense cicatrical matrix in which the sympathetic ganglia were embedded. From this point onward the gross appearance of the ganglia remained unchanged until the ninetieth day when the experiment was terminated. No visible changes were found in the control animals infiltrated with saline solution.

Microscopy.—

Novocain infiltration: At 3 days the majority of the ganglion cells were completely destroyed and replaced by empty cell capsules. Each damaged ganglion cell was reduced to an irregular shrunken anucleated structureless mass (Fig. 2, *A*.)

All forms of retrograde change such as vacuolization and hydropic alteration were observed in the surviving cells. Of some of the sympathetic cells only the nuclear membrane and an agranular nucleolus were seen. The gangliar capsule was thickened and the arteries and veins in this region were dilated and congested. No changes were observed in the caliber or in the endothelium of the intragangliar capillaries or arteries. The interstitial connective tissue was hyperplastic and arranged in coarse bundles.

At 7 days the predominant type of ganglion cell observed was large and hyperchromatic. The cytoplasm was sometimes structureless or sometimes contained fine perinuclear chromidial granulations. The nucleus was vesicular and was usually situated at the periphery of the ganglion cell. The nucleolus was the only structure always present. The interstitial connective tissue was hyperplastic and its arrangements in coarse bundles persisted. At 14 days (Fig. 2, *B*), the first signs of regeneration appeared. Some sympatheic cells appeared normal while others were heavily loaded with pigment, especially at the periphery of the sympathetic ganglia. Shrunken, irregular, hyperchromatic cells were predominant. The pigment was so abundant that it completely covered the nucleus. In some cells the cytoplasm was normal in color and contained numerous chromidial granulations while the centrally located nucleus was of normal structure. The cell membrane was normal and sometimes thickened. The amount of interstitial connective tissue was reduced. Neuronophagia was found in some of the cells. Globular hyperchromatic cells with short or long multiple dendrites were also observed.

At 21 days (Fig. 2, *C*), the histologic picture remained essentially similar to that observed at 14 days. Thirty days after the infiltration of the ganglia with Novocain many apparently normal sympathetic cells occurred whose cytoplasm contained numerous evenly scattered chromidial bodies. The nucleus and nucleolus were normal in size and full of chromidial granules. Scattered among the cells of normal appearance were an equal number of heavily or moderately pigmented cells.

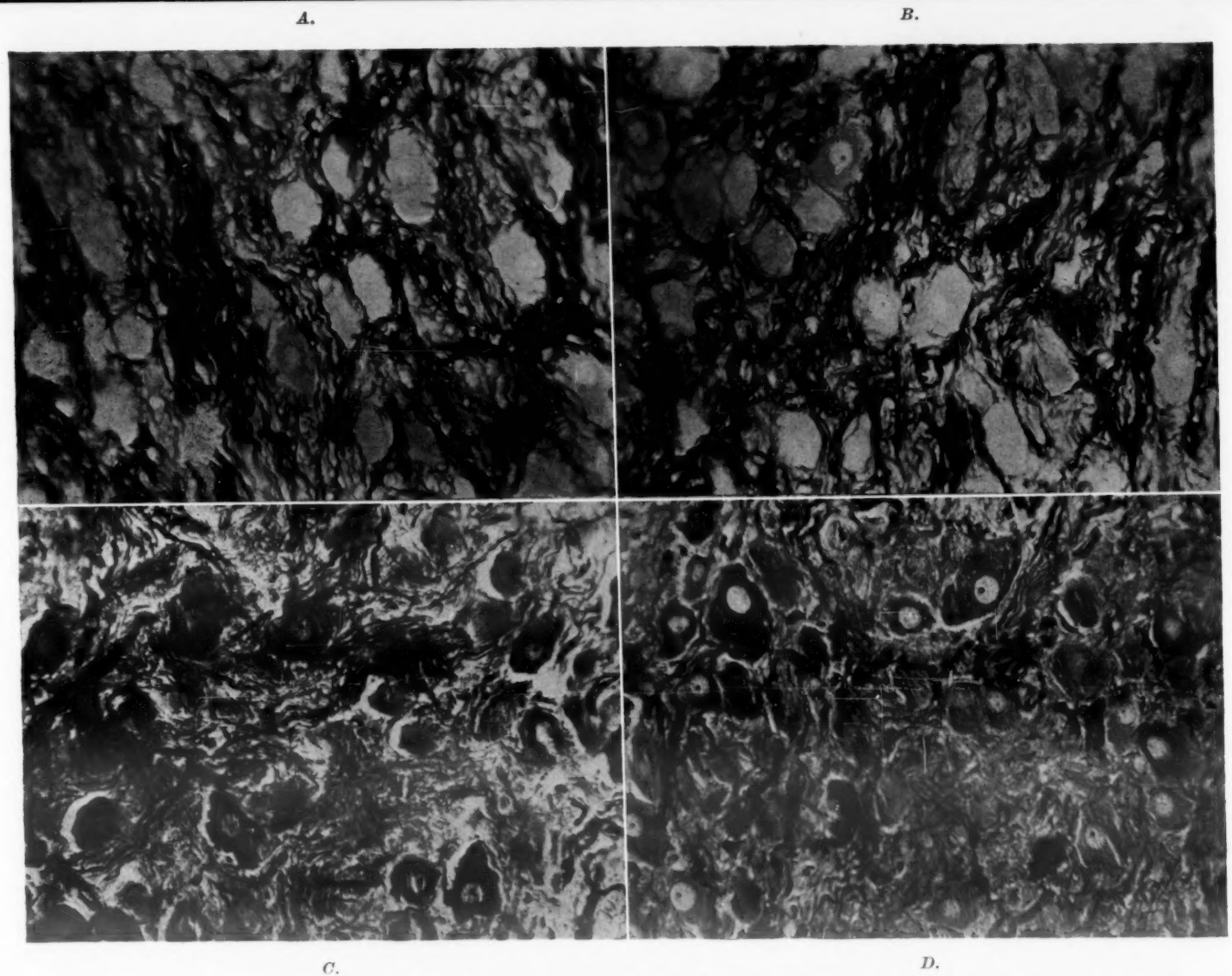


Fig. 2.—Novocain infiltration. *A*, 3 days. The majority of the ganglion cells are destroyed and replaced by empty cell capsules. Vacuolization and hydropic alteration are also seen. Silver impregnation.

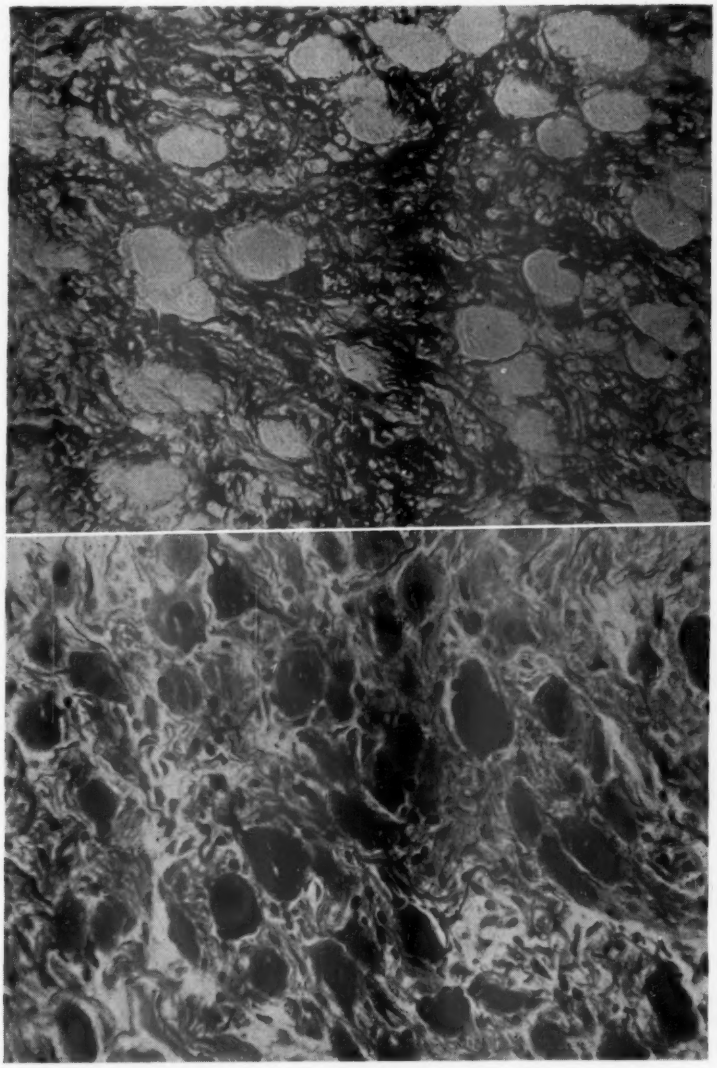
B, 14 days. First signs of cellular regeneration. Retrograde changes present. Silver impregnation.

C, 21 days. Predominance of shrunken hyperchromatic cells of normal appearance. Silver impregnation.

D, 45 days. Heavily pigmented and some sympathetic gangliar cells of normal appearance. Silver impregnation.

Other heavily pigmented cells with short or long thickened and deformed dendrites were observed. No trace of cellular disintegration or of neuronophagia were found at this stage. The interstitial connective tissue and the intragangliar vessels appeared normal. From this point until the termination of the experi-

A.



B.

Fig. 3.—Phenol infiltration. *A*, 3 days. Complete destruction of the sympathetic cells. Silver impregnation.
B, 30 days. Regeneration and heavy pigmentation of the gangliar cells. Silver impregnation.

ment the histologic picture remained essentially the same (Fig. 2, *D*). The extremely numerous cells with heavy or light pigmentation remained a prominent pathologic characteristic.

Phenol infiltration: The anatomic changes observed after phenol infiltration are essentially similar to, and more accentuated than, those seen after Novocain infiltration. For the first 7 days following phenol infiltration no trace of

organized sympathetic cells was found (Fig. 3, *A*). The destruction of the sympathetic cells was so complete that even the minor forms of cell degeneration were absent. At 7 days the majority of the sympathetic cells were colorless, structureless, and agranulated as in the case of Novocain infiltration. The cells were large and edematous and some were hyperchromatic with a vesicular nucleus. The interstitial tissue was hyperplastic.

At 14 days signs of regeneration were observed and apparently normal cells occurred while hyperchromatic and irregular cells were also present. The periganglíar capsule was thickened and large veins and capillaries full of blood

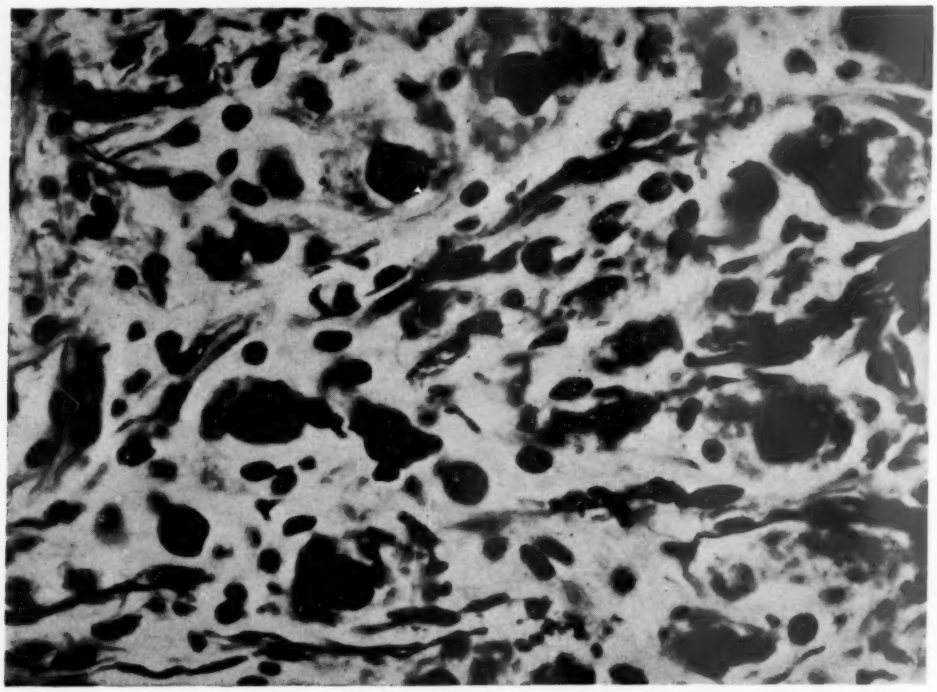


Fig. 4.—Saline infiltration, 24 hours. No deviation from normal is observed. Silver impregnation.

were in evidence. At 21 and 30 days pigmented cells were predominant (Fig. 3, *B*). Cells with all grades of pigment deposition were scattered among sympathetic cells of normal appearance. From this point onward the histologic aspect remained unchanged, the sympathetic ganglia never acquiring a normal appearance until the end of the experiment.

Saline infiltration: In the animals infiltrated with a normal saline solution no anatomic changes were visible after 6, 12, 24, and 48 hours (Fig. 4).

DISCUSSION

Various anatomic lesions of the sympathetic ganglion cells are reported. A number of investigators have attempted to correlate these changes with specific disease processes, while others found them to be within physiologic limits (Craig and Kernohan[1]). Shrinkage of the autonomic ganglion cells is encountered in carcinoma and in cachectic states. Vacuolization was observed to be

associated with retrogressive changes by Kuntz.[9] Hyaline degeneration was reported in chronic lead poisoning,[4] poisoning with sulfuric acid,[17] paralysis agitans, and chronic morphinism.[5]

Variations in the quantity and distribution of the chromidial substance in human sympathetic ganglia were also observed by Kuntz.[8-10] Complete disintegration of the chromidial bodies in infectious diseases was described by Mogilnitzky,[15] while Dolley[2, 3] and Ingersoll[7] correlated the modifications observed in the chromidial substance with cell activity and depression.

We observed changes in the cytoplasm and nucleus, and in the form and size of the ganglion cells, variations in the quantity and disposition of the chromidial substances, and in the thickness of the cell membrane, and finally changes in the quality and distribution of the interstitial connective tissue. The changes observed in the autonomic ganglia seem to suggest that the therapeutic action of Novocain may also be based on hitherto unsuspected anatomic changes.* It is not yet possible to interpret neural lesions in terms of modified function or to correlate them with a specific disease process. However, in view of the severe lesions observed, it is possible to assume that the gangliar cells have been destroyed by the infiltration of Novocain or phenol and have temporarily lost their physiologic function. The later occurrence of regenerative forms and cells of normal appearance may be assumed to indicate that some synapses are re-established at this period, permitting a partial relaying of efferent impulses. The presence and persistence of heavily pigmented cells for from 3 weeks to 3 months after the infiltration of the ganglia might be considered to indicate that the ganglionic cells were still in a state of functional depression and that the anatomic integrity of the ganglia was not completely re-established. The changes observed following Novocain infiltration were essentially similar to those described by Merrick after intragangliar alcohol infiltration. The effect of Novocain differs from that of alcohol in that regeneration following alcohol infiltration begins after a longer period of time and is complete at 90 days. This comparison appears of interest since it indicates that the action of Novocain is possibly of longer duration than that of alcohol. This raises the question whether, in spite of its disadvantages[21] (neuritis, pleuritic pain, etc.), the use of alcohol to obtain greater cell destruction and better clinical results is justified.

In the light of our experiments Novocain appears to have the advantage of completely destroying the sympathetic ganglion cells without the secondary irritative phenomena produced by alcohol.

SUMMARY

1. The intragangliar infiltration of the superior cervical ganglia with small quantities (0.3 c.c.) of 1 per cent Novocain or with an aqueous solution of 6 per cent phenol causes widespread damage to the sympathetic ganglion cells in cats. No visible changes were observed when a normal saline solution was used.

*It is difficult to believe that the widespread changes observed in the sympathetic ganglia are the results of the trauma produced by the needle during the injection or by the small amount of substance injected. Moreover, ganglia injected with the same amount of normal saline solution fail to show any visible deviations from the normal.

2. The destruction of the sympathetic ganglion cells is complete during the first 2 weeks following Novocain or phenol infiltration. Signs of regeneration begin to appear between 2 and 3 weeks after infiltration, but the anatomic structure of the sympathetic ganglia is not completely re-established by the ninetieth day.

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A CRITIQUE ON THE REPAIR OF HYPOSPADIAS

DONALD R. SMITH, M.D., AND HARRY M. BLACKFIELD, M.D.,
SAN FRANCISCO, CALIF.

(From the Departments of Urology and Surgery, University of California School of Medicine)

NOT only has there been a renewed interest in the repair of hypospadias during the past ten years, but many of the papers which have espoused a method of cure have included publication of the number of boys submitted to surgery as well as a critique of complications (Table I). This has allowed the student of the subject to judge better for himself which method or methods seem sound. Too many articles, however, still fail to cite the number of patients treated by the operation which they describe and it is probably safest to assume they are written about one case only unless one has knowledge to the contrary. Some of the most unsound methods have worked once!

It seems proper at this time to evaluate the most promising plans for correcting the chordee as well as those suggested for the formation of an adequate urethra.

CORRECTION OF THE CHORDEE

First of all, we find it necessary to explode the myth about the presence of a "bowstring" of rudimentary corpus spongiosum, extending distal to the abnormally placed orifice, as the cause of the chordee. Every article on this subject pays homage to it and medical illustrators dutifully depict it as a heavy, broad, fibrous band which the surgeon must excise. We have corrected the ventral curvature in forty-six boys and have seen it only three times and these were in patients with perineal hypospadias. We will go even further and state that the other forty-three patients had perfectly normal corpora spongiosa extending from the abnormal orifice to the glans.

The spongiosum occupies the midline and its covering fascia is not scarred. If it is nicked during dissection, its spongy nature is obvious; nothing else bleeds quite so profusely. Often, however, minor bands of fibrous tissue, which may contribute to the chordee, may be found at either border of the spongiosum where it meets the corpora cavernosa.

We believe that, in most instances, the chordee is present because the thin skin distal to the hypospadiac orifice is firmly stuck to the fascial sheaths of the corpora. This skin lacks subcutaneous tissue and must be freed from the shaft by sharp dissection. Once this is accomplished, the penis is straight or almost so. On occasion, on the ventrolateral surface, as we have pointed out, there may be minor fibrous bands which are most easily discovered by scratching the entire ventrum with the tip of the scalpel with the penis held in extreme dorsiflexion. If they are demonstrated they should, of course, be resected.

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TABLE I. NUMBER OF OPERATIONS AND COMPLICATIONS REPORTED ON BY VARIOUS AUTHORS

	NUMBER OF FISTULAS	PER CENT WITH FISTULAS	NUMBER OF COMPLETED CASES	
Urethroplasty using penile skin				134
Byars (Duplay)	12	23	52	
Creevy (Thiersch-Duplay)	4	44	9	
Culp (Cecil)	0		19	
Smith-Blackfield (Blair)	8	38	21	
Smith-Blackfield (Blair-Wehrbein-Duplay)	4	18	22	
Wehrbein	3	27	11	
Nové Josserand (free inlay graft)				80
McIndoe	Not stated		35	
Havens-Black	Not stated		29	
Young-Benjamin	11	69	16	
Duplay-Marion (subcutaneous skin strip)				50
Browne	3	6	50	
Ombrédanne				86
Schaefer-Erbes	0		25	
Loughran	4	13.8	29	
Walters	4	12.5	32	
Total				350

It is obvious, then, that only an operation designed to completely denude the ventrum can possibly allow of the proper reduction of the chordee. The methods described by Edmonds, Blair, and Nesbit accomplish this admirably. The Edmonds procedure, however, has the disadvantage of requiring two operations, though the first is quite minor. The operations of Blair and Nesbit are essentially the same except that Blair makes a long dorsal slit down the redundant foreskin and the flaps which are thus developed are swung onto the ventrum while the Nesbit procedure allows a shift of preputial skin to the ventrum by buttonholing the foreskin through which the glans is slipped.

We have used Blair's method in all our cases and find it most satisfactory. Byars also favors this procedure. It allows of more accurate "fitting" since the preputial flaps can be swung to the ventrum and if more skin is needed, the dorsal slit can be further deepened.

In any event, we are convinced of one fact, namely, that the so-called Heineke-Mikulicz maneuver (first described by Duplay) should be abandoned. It is ill designed for correction of the chordee and the longitudinal closure of the incision adds length but at the expense of the circumference of the skin whose adequacy is vital.

FORMATION OF THE URETHRA

1. *Urethroplasty Formed From Skin of Penis.*—This is probably the most common method employed for the formation of the urethra. By means of a U-shaped flap outlined on the ventrum, with its parallel incisions joined just proximal to the hypospadiac orifice, the urethral meatus is advanced to the region of the frenum. This operation has fallen into disrepute because the denuded ventrum has been covered by drawing the lateral penile skin flaps over the new urethra (Duplay). Even the Thiersch or Cecil modifications have failed

to yield satisfaction. Multiple fistulas have been the rule (Creevy, Charnock, and Kiskadden). If only penile skin is used for both the urethroplasty and the ventral cover, there must be limitation in the width of the flap outlined for the urethra else the lateral flaps will not meet in the midline. This operation therefore presupposes a new urethra of inadequate caliber. Its worst enemy, however, is tension on the suture line, though many authors blame infection or erections for their sloughs and fistulas. The fact that the penile integument develops marked edema in the immediate postoperative period must be accepted and at the conclusion of any operation upon it, the skin must envelop the organ loosely. Various fancy stitches, bolsters, or antibiotics whether applied locally or parenterally cannot make up for the violation of this surgical principle. The juxtaposition of the suture lines of the covering skin and of the urethra further contribute to the formation of fistulas. The Thiersch modification causes these suture lines to be in different planes but tension still defeats it and the caliber of the urethra thus formed must, of necessity, be small.

Byars, whose series, comprising fifty-two patients, is the largest so far reported, is the only surgeon who has enjoyed success with this method. By using the Blair operation for correction of the chordee, he does develop some redundancy of penile skin which is absolutely essential if this type of repair is to be successful. His urethroplasty is a classical Duplay type; he does not, ordinarily, primarily anastomose the new urethra to the abnormal orifice. This is left for a third stage. He makes the urethral flap equal to one and one-half times the expected circumference of the new urethra and closes it with a running suture of fine catgut. The lateral skin flaps are brought together with multiple tiers of skin sutures which tend to neutralize the effects of juxtaposition of the suture lines of the urethra and of the covering skin. Byars, however, does not state the caliber of the urethra thus formed. Thirty-three of the fifty-two patients were operated upon successfully in three stages while seven of the repairs were completed in two operations by combining the second and third stages. Twelve patients (23 per cent) developed fistulas which required later closure.

2. *Urethra Formed From Ventral Penile Skin Using Scrotal Skin as a Cover.*—The formation of an adequate urethra from the ventral skin is most feasible if the denuded ventrum is covered by skin from some other area. If this is done, there is almost no limit to the amount of skin which may be included in the urethral flap. A urethra of adequate diameter can then be formed for this skin can be replaced by the transplanted skin. The scrotum is an admirable source for this integument for it is close at hand and is blessed with the required resiliency. Three operations have been described which fulfill these principles.

A. Blair published his plan for a Duplay urethroplasty using an L-shaped flap of scrotal skin as a cover. We modified it in a few minor ways and our experiences have been previously published. This operation afforded a urinary channel of such size that urethral dilatations were never necessary. At the time of that report, we had completed the repair of hypospadias in fourteen boys and seven more have been thus treated subsequently. Thirteen (62 per cent) of the operations were uncomplicated, while in each of the remainder one

fistula developed. Six of these were closed without difficulty. The other two required two attempts before the fistulas were successfully closed. There were, then, no failures. The Blair operation, however, requires three operations.

B. Wehrbein, in 1943, described his method for the cure of hypospadias which consists of a urethra of the Duplay type with a ventral cover of scrotal skin which is previously prepared as a tube pedicle in conjunction with the first stage. This is a much simpler operation than that of Blair and requires only two stages. Wehrbein reported on the repair of hypospadias in 11 boys and 8 (73 per cent) healed without fistula formation. Later, Goodhope described the same operation. Since 1947 we have completed the repair of hypospadias by this method in twenty-two patients. The results will be discussed in detail below.

C. Cecil, in 1946, published a method which is similar to that of Blair except that he covers the new urethra with flaps of skin raised from each side of the scrotum rather than from just one side. The principles underlying it are sound but it, like the Blair procedure, requires a third stage at which time the penis is freed from the scrotum. The only series utilizing this method has recently been published by Culp. He corrects the chordee after a method described by Young which allows of fairly satisfactory exposure of the ventrum and shifts preputial skin onto the shaft. A Duplay urethroplasty is done at the second stage. A midline incision is then made in the scrotum allowing the raw surface of the penis to be buried in the scrotum. The skin edges of the scrotum are sutured to those of the penis. A third operation is necessary to free the penis from its scrotal attachments. Culp is usually able at this time to cover the new urethra with penile skin only. His series comprised nineteen cases. Three patients developed fistulas which, however, closed spontaneously. This is the most successful series so far reported, but a few permanent fistulas are inevitable.

3. *Urethra Made From a Free Inlay Graft.*—The use of the free inlay graft described by Nové Josserand fell into disrepute because of the frequency of strictures and fistulas. Recently, McIndoe, Havens and Black, and Young and Benjamin have revived the operation. A split-thickness graft is obtained from a nonhair-bearing area and wrapped around a tube with the raw side out. The ventrum of the penis is tunneled subcutaneously with a trocar which emerges at the tip of the glans and the graft, on its tube, is placed therein. Havens and McIndoe leave a dilator in this new urethra for six months so it will maintain its caliber. Then the new urethra is anastomosed to the abnormal orifice. Young anastomoses the inlay graft to the hypospadiac opening, primarily.

A critical analysis of their work is most instructive. Havens follows McIndoe in using the Edmonds operation for correction of the chordee. This operation has no advantage over the Blair or Nesbit procedures yet it requires two stages. Young and Benjamin state that they rarely use any foreskin when they correct the chordee though at the same time they stress the need for "plenty of skin on the ventrum." This is difficult to understand, for correction of the chordee of necessity increases the area of the ventrum.

Havens and Black wait until the patient is 16 years of age before the inlay graft is placed, McIndoe chooses to do this operation when the child is 7 or 8 years old, while Young and Benjamin recommended 2 or 3 years as the age of choice. It is well known that split-thickness grafts tend to contract both longitudinally and transversely. It is also obvious that these grafts lack the looseness and resiliency of penile skin. It seems a lot to ask for these grafts to keep abreast of the growth associated with puberty and still have enough to accompany an erection in adult life without ventral curvature. Havens and Black must have this in mind when they delay this urethroplasty until the age of 16. Young and Benjamin do say that the final answer to this will come when their patients reach adulthood. Until such a time arrives, one must give these theoretical objections some consideration.

McIndoe and Havens leave a dilator in the new urethra for 6 months in order to avert circumferential contracture. This it apparently accomplishes but it would seem that all contracture of this graft must then take place in the longitudinal plane which might then increase the chance for significant chordee. It would seem better, on theoretical grounds, to place a free graft urethra of a caliber of 50 per cent larger than that which is planned for the final diameter, thus circumventing the need for an indwelling dilator. Young apparently does just this for he finds a dilator unnecessary.

The operation described by McIndoe, and which is followed to the letter by Havens and Black, requires a minimum of four separate procedures, though the first is minor. The correction of the chordee requires two operations, followed by the inlay graft which later must be anastomosed to the abnormal orifice. McIndoe, unfortunately, does not state how many of the final procedures were unsuccessful thus necessitating repair of fistulae (that is, a fifth or even sixth operation). Havens and Black describe the proper method for their repair, but again, their incidence of fistulas is not stated. We may presume they are not uncommon.

Fortunately, Young and Benjamin do tell us what we want to know about their method. They choose to correct the chordee when the boy is 12 months old and this they accomplish in one stage. The inlay graft is placed at the age of 2 or 3 and at that time the grafted urethra is anastomosed to the hypospadiac opening. Of sixteen cases so treated, only five (31 per cent) healed without fistula formation. Each of the remainder had one fistula, though three were considered so small that closure was not attempted. Fifty per cent of their patients required a third operation for closure of fistulas and three of these failed. This experience points up the difficulties which may accompany the closure of urethral fistulas.

One of the main advantages of the Nové Josserand operation over the Duplay urethroplasty is said to be that the urethra opens on the tip of the glans. It is interesting, however, that the men championing this operation do not recommend repair of glandular hypospadias. They apparently consider this defect functionally normal. So do we.

This type of operation, however, is the only one so far described which will furnish a nonhair-bearing urethra in the mid-scrotal and perineal types of

hypospadias. We have developed a four-stage repair of such defects which consists of (1) correction of the chordee, (2) free inlay graft urethra in the perineum or scrotal area (where added length is not needed during an erection), (3) anastomosis of the perineal urethra and the hypospadiac orifice, with the formation of a tube pedicle on one side of the scrotum (Wehrbein) and (4) the formation of a Duplay urethroplasty using the tube pedicle as a ventral cover. This will be published later in more detail. There is no doubt that the Nové Josserand operation would be simpler for these advanced defects but until time and experience show that a free-graft urethra can be applied to these cases without chordee occurring with erections, we will continue to utilize our more complicated procedure. Simplicity of repair is second in importance to the accomplishment of the ideal repair in all cases of hypospadias.

4. *Operation of Duplay-Marion: Urethra Formed From Strip of Buried Penile Skin.*—In 1880, Duplay published an article on the repair of hypospadias which was quite different from the one with which we ordinarily associate his name and which had appeared in the literature six years earlier. He made two longitudinal incisions on the ventrum of the penis but did not undermine their edges and form a closed tube. Instead, he pierced the glans with a trocar and passed a catheter through it so that the catheter lay on this midline skin strip. The lateral skin flaps were then widely undermined and their edges broadly approximated over the catheter. The illustrations in this article clearly show this as well as the employment of double-locking sutures and the interrupted sutures in the skin edges. He also mentioned that he no longer found it necessary to make a long dorsal relaxing incision. It is interesting, however, that he had employed it. At another operation, he anastomosed the new urethra to the hypospadiac one.

In 1936, Cecil cited this method and in 1942 Marion and Pérard discussed it in detail since they considered it the operation of choice for the repair of hypospadias. They performed the operation in two stages by forming a complete urethra at the second stage. Apparently they did not find the dorsal relaxing incision necessary.

Denis Browne has recently resurrected this operation in all its aspects. It is curious that he cites no bibliography in his two papers. He reports rather startling results with the Duplay-Marion operation and, since it seems to violate some fundamental principle of surgery, it requires critical consideration.

In order to correct the chordee, he makes a transverse incision on the ventrum just proximal to the glans. This is extended into the prepuce laterally. The fibrous tissue is divided and allowed to slide proximally and the skin incision is closed longitudinally. In order to relieve tension, a long dorsal incision is made and the skin edges are allowed to separate. This defect is allowed to granulate in and re-epithelize.

At the second operation, after diversion of the urine by means of a perineal urethrocystostomy, the strip of midline ventral skin is outlined. The width of this flap in relationship to the circumference of the penis is not mentioned but judging by his illustrations, it cannot equal more than one-sixth of the circumference of the penis. The adequacy of the urethra which is thus developed is

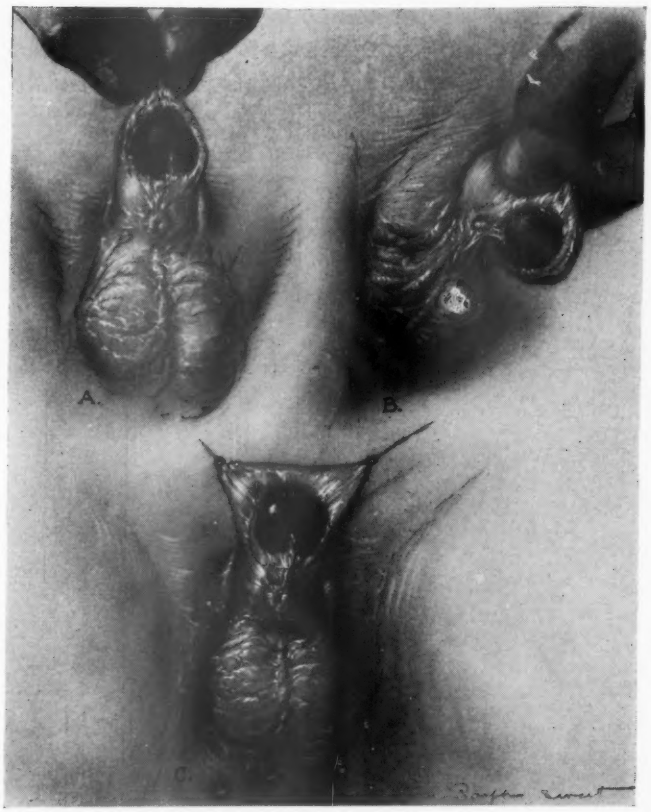
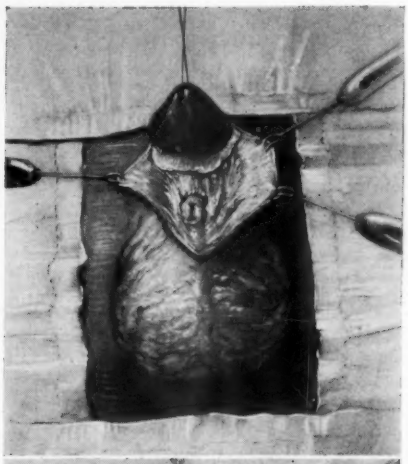


Fig. 1.—First stage. Typical deformity of hypospadiac penis showing ventral chordee, abnormally placed meatus, and hooded dorsal foreskin. Dotted lines indicate incision.

Fig. 2.—Circumferential incision just proximal to corona. Foreskin is dissected from the shaft. Note that all flaps are handled with small double hooks. The use of "eye" scissors for this dissection is suggested. (From Smith and Blackfield: J. Urol., 1948.)

immediately in question. While it might be argued that such a flap of penile skin finally allows the devolpment of a urethra of a circumference much larger than the width of the original skin flap, it is interesting that Nesbit, in a series of experiments utilizing buried skin strips in rats and dogs, found that the circumference of the epithelized tubes was about equal to the width of the original flap. Then, in order to bury this strip, the lateral skin flaps are brought

Fig. 3.



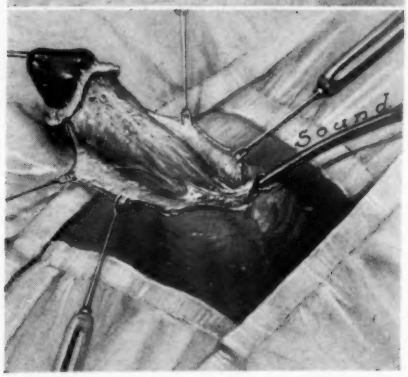


Fig. 4.

Fig. 3.—Incision carried proximally on ventrum surrounding meatus and extending just beyond it. A considerable cuff of skin should be left about meatus so that suture lines do not encroach too closely upon it; meatal stricture might result. Skin flaps are freed by dissection with small scissors. The skin distal to the meatus is thin and usually plastered to underlying tissue. This is the major cause for chordee. Fibrous bands between corpus spongiosum and corpora cavernosa should be sought and resected. (From Smith and Blackfield: J. Urol., 1948.)

Fig. 4.—Elongation of ventrum has been obtained. It may be necessary to free the distal urethra and shift it posteriorly to complete correction of chordee. (From Smith and Blackfield: J. Urol., 1948.)

over with wide approximation (one-half inch) of their edges. In order to obviate tension, a dorsal incision is again made from the glans to the root of the penis, the skin edges are allowed to separate widely and the raw area is left to granulate in.

Browne states that the area of the new urethra becomes quite soft after one or two years. If there is that much tissue reaction, it is difficult to believe that no scar or contracture occurs. He says that this operation can be used in all

degrees of deformity but it is obvious that if it is applied to midscrotal or perineal hypospadias, the posterior part of the flap must of necessity be hair-bearing. Only a split-thickness inlay graft in this area will satisfactorily answer this problem.

Fig. 5.

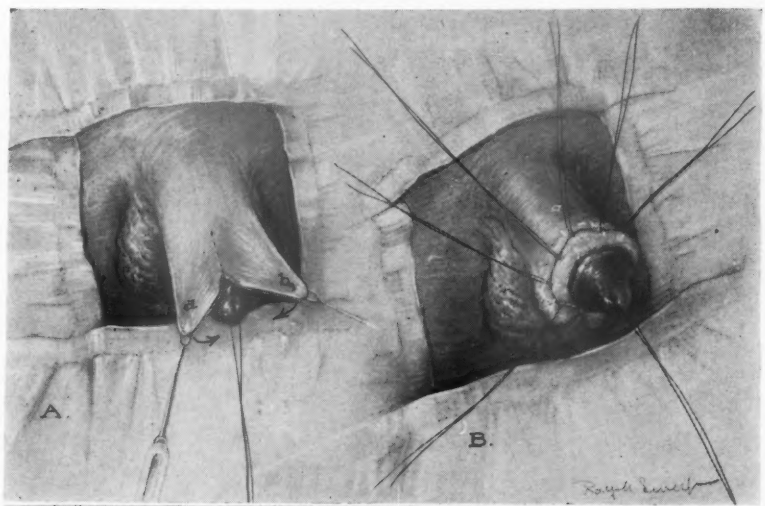


Fig. 6.

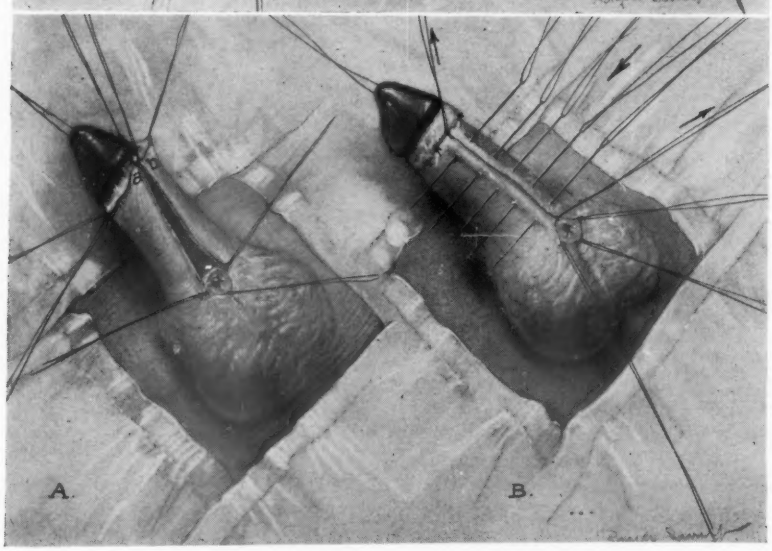


Fig. 5.—*A*, Area of ventrum thus increased requires more skin for cover. This is obtained by separating double fold of foreskin, thereby converting it into single layer. This redundant flap is split down midline 3 to 4 cm. so that *a* and *b* meet at frenum without constricting shaft, yet affording an adequate and loose cover for ventrum. If more is needed here, the dorsal slit is further deepened. *B*, Adjacent skin edges sutured. (From Smith and Blackfield: J. Urol., 1948.)

Fig. 6.—Ventrolateral skin closed; dorsal flaps *A* and *B* are now on ventrum. Note relative posterior displacement of meatus due to elongation of corpora. (From Smith and Blackfield: J. Urol., 1948.)

In three of the fifty cases reported by Browne, fistulas developed. Two of these three boys had been operated upon by other surgeons who, we presume, contributed a minority of the cases. In other words, a significant incidence of

fistulas is to be expected in most hands. It should be noted that Byars who also employs wide approximation of the covering skin over a completely formed urethra, reports fistulas in 23 per cent of his cases. It is difficult to see how the buried skin-strip operation should enjoy a significantly smaller number of fistulas. Marion and Pérard discuss the technique for closing fistulas which fact suggests that they are not rare.

Fig. 7.

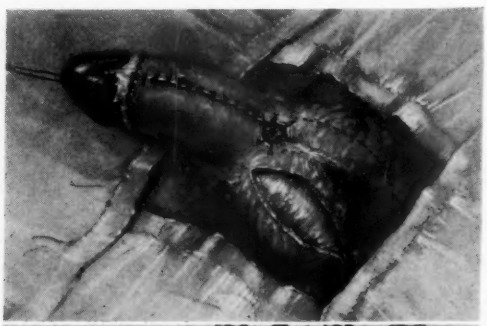


Fig. 8.

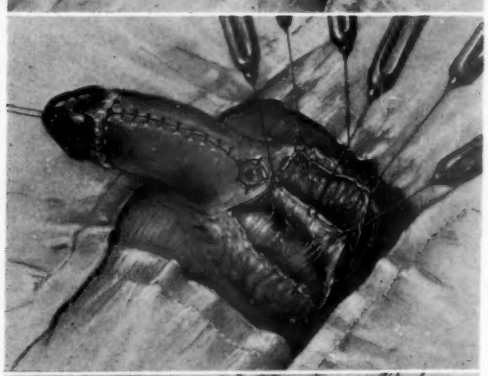


Fig. 9.

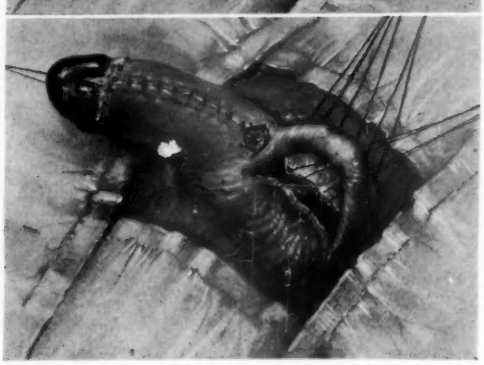


Fig. 7.—Formation of scrotal tube pedicle. The width of the flap is equal to one-half the circumference of the penis and should be marked out without any traction placed on the scrotum. A tube too small in diameter is worthless.

Fig. 8.—Skin strip being freed from the scrotum.

Fig. 9.—Formation of the tube pedicle. A pressure dressing is applied with the penis in the dorsal position. The dressing and the catheter are removed in 8 days.

THE BLAIR-WEHRBEIN-DUPLAY OPERATION

Our previous experiences with the modification of the operation devised by Blair were most satisfactory. For purposes of comparison, an analysis of our twenty-one patients treated by this method seems in order. Thirteen (62

per cent) healed cleanly and without fistula formation. Of the remaining eight, one developed two fistulas, the others, one each. All fistulas formed at the site of the abnormal orifice. Six of these were closed successfully in conjunction with the third stage procedure so this complication added no extra operations. Thus, nineteen of the twenty-one patients (90 per cent) had their repairs completed in the three stages as planned. Each of the other two boys required a fourth operation before their fistulas were cured. Since we started this series 12 years ago, we are in a position to state that in adulthood erections are excellent and without chordee. All in all, this method of repair compares quite favorably with any so far presented.

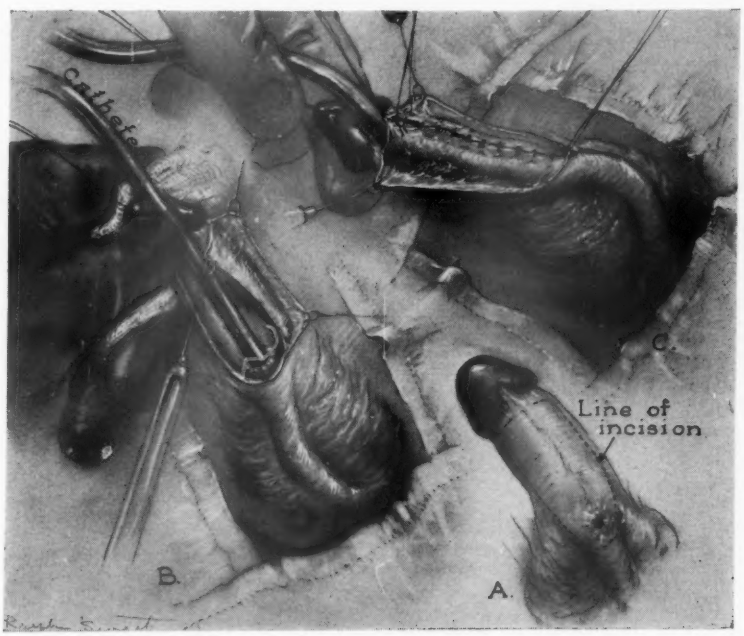


Fig. 10.—Second stage. A U-shaped incision is made and edges of central strip slightly undermined. A small catheter is placed in the bladder. Urethra is formed with Lembert sutures of 0000 ureteral gut on atraumatic needles. Urethra in region of abnormal meatus should be further reinforced with a second suture layer for this is the site of the occasional fistula.

In 1947, believing that the operation described by Wehrbein was sound and offered a two- instead of a three-stage procedure, we changed our technique. We continue to use Blair's first-stage operation (Figs. 1 to 6) but, in conjunction with it, a tube pedicle is formed from the scrotal skin as well (Figs. 7-9). We still choose the age of 18 months as the optimum time for this correction.

When the child is 4 years old, well before the school age, or from three to six months after the first operation if he is older, the final stage is executed. It consists of a Duplay urethroplasty with the width of the flap equal to from one-third to one-half of the circumference of the penis (Fig. 10). The denuded ventrum is then covered by the scrotal pedicle (Figs. 11 and 12). We have not found it necessary to "season" the pedicle by periodic occlusion of its distal end.

In these four years, we have operated upon twenty-six boys using this plan. Twenty-two have had the operations completed, while four have had the first stage only. Of the twenty-two, eighteen healed without fistula formation (82 per cent). One of the four boys had two fistulas, while the remainder had one. Three patients had their fistulas repaired by one operation, while one required an additional attempt before success was achieved. The four who developed complicating fistulas, then, enjoyed successful repair. Most of these operations

Fig. 11.

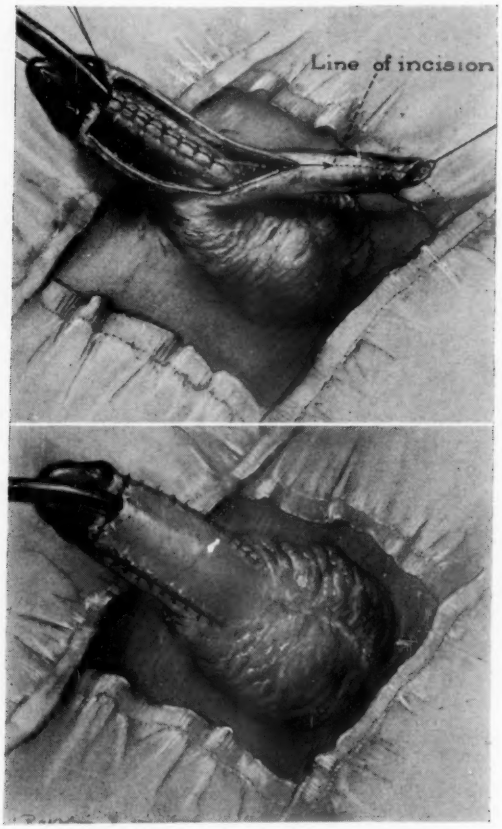


Fig. 12.

Fig. 11.—Distal end of the tube divided. A cleavage plane is formed down its core with small dissecting scissors and the tube opened.

Fig. 12.—Flap is hinged at penoscrotal junction, placed on ventrum, and sutured to lateral and distal skin edges. There is no juxtaposition of urethral suture line and that of covering skin. Pressure dressing is applied with penis in dorsal position. Catheter and dressing are left on 8 days.

have been performed by our resident staff, thereby demonstrating that the success of this procedure does not depend upon the skill of one experienced operator but must be attributed to the soundness of the principles employed.

At the outset, we practiced diversion of the urinary stream through a perineal catheter; six years ago we gave this up. We have not found that it enhances the result or mitigates against fistula formation. Vesical drainage is accomplished by a small catheter placed in the new urethra. We do not fear

Fig. 13.—D. K., age 3 years. *a* and *b*, Typical chordee and midshaft hypospadiac orifice. *c* and *d*, Six months after first stage. Chordee is now corrected and the orifice is now penoscrotal. Note the tube pedicle on the scrotum. *e* and *f*, Appearance 9 days after the second stage. Note the absence of reaction and edema. *g* and *h*, One month after the second stage. Orifice is at the frenulum; there is no chordee. Notice redundancy of tissues which are soft and without induration.

erections for there is no skin tension. We have not depended upon chemotherapeutic or antibiotic agents nor have we any personal proof that they are of any value; they will not counteract the effects of tension. The patient who developed two fistulas had no diversion of the urine by any method but was allowed to void immediately through the new urethra. We believe that this is a poor practice. Experience, however, shows that fistulas are closed most satisfactorily without the employment of urinary diversion or retention catheter.

SUMMARY AND CONCLUSION

The satisfactory repair of the hypospadiac penis requires that in adulthood the patient have a straight penis when erected, and a urethra of normal caliber that is free of hair. Preferably, the urethra should be of constant diameter throughout its length. The operative procedures should not demand too much in the way of special skills on the part of the surgeon.

We do not feel that the Ombrédanne operation meets all these requirements, nor are we sure that the procedure revived by Browne will stand the test of time. We question the caliber of the urethra which is formed and worry about the extensive dorsal incisions which are allowed to granulate in. We have had enough experience with the repair of hypospadias to know that penile skin can form scar.

The operation of Nové Josserand (the urethra formed from a free inlay graft) offers much, but the incidence of fistulas is probably not lessened. Further, some longitudinal contracture must be expected and one wonders whether the new urethra will parallel postpuberty penile growth if this procedure is practiced in the young. The final question is whether in adulthood there is enough elasticity of the urethra to allow of a straight erection. These questions are answerable and undoubtedly will be clarified in the future.

The use of penile integument for the new urethra is logical because one can expect its growth to parallel that of the penis. This allows of its application in children. We also know that such a urethra maintains its elasticity and that erections, later, are straight. We believe that a urethra of adequate diameter can be constructed only if covering skin is obtained from somewhere else and the scrotum is the logical site for this. Such a plan also allows the surgeon to stagger the suture lines of the skin cover and that of the underlying urethra thereby lessening the incidence of fistulas. Only Byars has been successful in violating this principle.

We have repaired forty-three cases of hypospadias using methods (Table I) which fulfill these tenets. The final results have been functionally excellent and the incidence of fistula formation has been relatively low. We have found the Blair-Wehrbein-Duplay procedure to be simple and it offers a two-stage operation whereas the original Blair and the recent Cecil operations require three.

It is hoped that in the future all authors reporting on this subject will state the number of patients upon whom they have operated, and the type and incidence of complications. It is only through such analyses that final judgment concerning the best method for the repair of hypospadias can be made.

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REMOVAL OF THE LIVER OF THE DOG: AN EXPERIMENTAL SURGICAL TECHNIQUE

JOHN H. GRINDLAY, M.D.,* AND FRANK C. MANN, M.D.,* ROCHESTER, MINN.

IN CERTAIN studies of the function of the liver and of its role in body metabolism, it is necessary to remove the organ. Several excellent techniques have been developed to perform total hepatectomy in dogs. The basic principle of these techniques is the creation of the means for blood to return to the heart from the portal vein and inferior vena cava without its having to traverse the liver. The standard technique devised by one of us (Mann) and used in our laboratory for many years requires two preliminary operations. At the first operation a reverse Eck fistula, that is, a side-to-side portacaval anastomosis and ligation of the inferior vena cava between the liver and the anastomosis, is made. The effect of diverting blood from the vena cava into the portal vein, thence into the hepatic sinusoids, is to raise pressures in the cava and to encourage blood to flow through small abdominal wall veins and retroperitoneal veins which connect with veins draining toward the superior vena cava. Enlargement of such collateral veins gradually occurs and, usually in about two months, these veins are sufficiently large that the second operation may be performed, namely, occlusion or constriction of the portal vein between the portacaval shunt and the liver. Thus, all or most of the portal blood is diverted into the vena cava through the portacaval shunt and must pass through the collateral veins which the latter has developed, and which now undergo further enlargement. Within a month and at any time thereafter the liver may be removed. The dogs remain in good general condition and require no special care. When hepatectomy is performed, the livers usually appear normal, both grossly and histologically. The liver is exposed for hepatectomy through a midline abdominal incision and is removed by dividing the gastrohepatic ligament and omentum, the vena cava below the liver, diaphragmatic ligaments and, finally, the vena cava below the diaphragm.

A technique which requires one, or more often two, preliminary procedures was described by Markowitz and Soskin. In the first procedure ligatures of heavy cord are tied about both the portal vein and the vena cava close to the liver so as to reduce the diameter of the vessels to one fifth. The mortality from this operation is high, and a second operation at which the vessels are completely ligated is usually necessary before hepatectomy. This method causes the formation of a good collateral circulation, but removal of the liver in the final procedure through an abdominal incision is usually difficult because of the presence of numerous vascular adhesions around the ligatures.

Other techniques which have been used are one-stage techniques and have in common two objectives: a means of bridging the defect in the inferior vena

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*Division of Experimental Medicine, Mayo Foundation, University of Minnesota.

cava created by excision of the portion within the liver, and a means of diverting blood from the portal vein to the cava. These methods are excellent but require considerable experience; hemorrhage and air embolism, as well as surgical shock, are the hazards. In the method of Firor and Stinson a Y-shaped tube of Pyrex glass is used; one limb of the Y is inserted into the portal vein, and the remainder of the tube is placed inside the vena cava in such a fashion that the end of the longest arm extends into the thoracic portion of the cava. Ligatures are placed about the vena cava near both ends of the tube but, as soon as the ligature next to the diaphragm is tightened and tied, the hepatic veins are blocked and the liver must be removed expeditiously. The method of Markowitz, Yater, and Burrows differs only in that the portacaval anastomosis is made by the usual suture technique and in that a straight glass tube is placed in the portion of the cava which traverses the liver.

Recently Nolf and Adant have described a one-stage technique of hepatectomy in which also a portacaval shunt is made; continuity of the vena cava is re-established by means of a graft—a length of thoracic inferior cava from another dog.

For more than a year we have used a method of total hepatectomy which seems to have the advantages of the three-stage technique of one of us (Mann) and which does not require the making of a portacaval anastomosis. The removal of the liver is easier and less hazardous than it is in the one-stage methods; the procedure can be performed in less than an hour and thus the liverless dog is left with a smaller dose of anesthetic agent from which to recover after operation than the dose required for one-stage methods.

Our method is a two-stage method. At the first operation the portal vein and the vena cava are constricted below the liver by narrow bands which cause gradual and eventually almost complete occlusion of the vessels within a period of six to eight weeks. As the rate of flow of blood through the constriction in each vessel steadily becomes less, more and more blood is made to flow through collateral veins which by-pass the strictures and lead to tributaries of the superior vena cava. When the process of rerouting of portal and caval blood around the liver has been completed, usually about six to eight weeks after the first operation, total hepatectomy may be performed as a second operation without interfering with return of blood from the viscera and lower extremities to the heart.

TECHNIQUE

We have used ether as the anesthetic agent and have employed the usual aseptic surgical technique for both the first operation and the final procedure, hepatectomy. The material that we have used to constrict the vena cava and the portal vein, a material which gradually causes nearly complete occlusion, is laminated cellophane tape.* The tape, which is red and is 6 mm. wide, is used commercially as the tear-tape for cellophane wrappings. Its advantages over strips of ordinary cellophane film are that it does not break easily even when it is tied in a tight knot. We have sterilized the tape by immersing it in

*The red laminated cellophane tape was kindly furnished by The Dobeckmun Co., P. O. Box 6417, Cleveland, Ohio.

1:1,000 benzalkonium chloride (Zephiran Chloride) solution for twenty minutes and have rinsed the tape in sterile physiologic saline solution before it was used. Edema of the adventitia of the vein about which the band is applied ensues and is followed by fibrous tissue thickening. Gradual contraction of the new fibrous tissue in the adventitia causes a progressive reduction of the diameter of the vein.

First Operation.—The vena cava and the portal vein are exposed (Fig. 1, *A*) through a midline abdominal incision extending from the xiphoid to below the umbilicus. The edges of the incision are held widely apart by a self-retaining abdominal retractor. Good exposure of the vena cava may be obtained

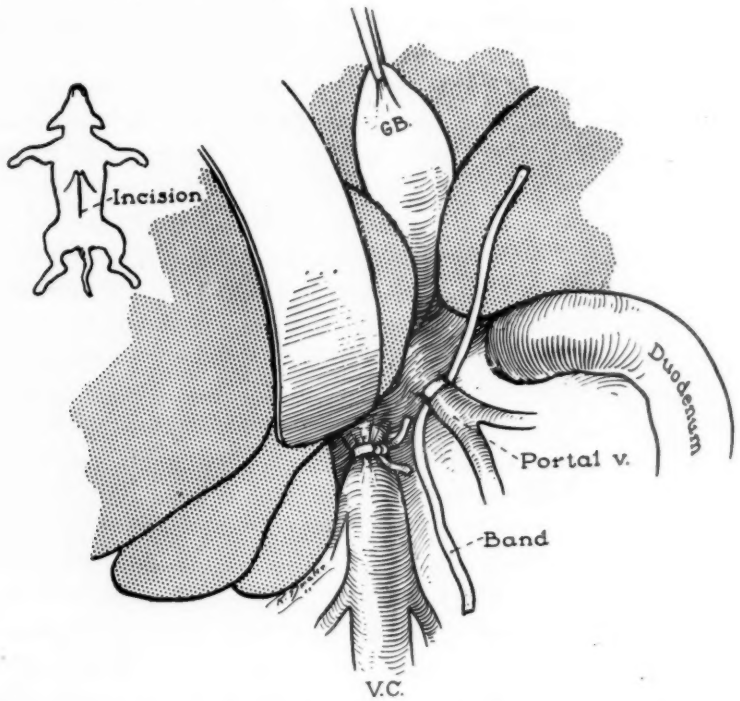

Fig. 1.—Technique of total hepatectomy. *A*, First stage of operation. The vena cava (V. C.) and the portal vein have been exposed just before they enter the liver. A laminated cellophane band has been placed on the cava, tightened, and tied. The band on the portal vein is ready to be tightened and tied. GB. is gall bladder.

by placing the loops of intestine on the left side of the abdominal cavity and covering them with the mesentery of the duodenum. The duodenum and its mesentery are then covered with a soft gauze or towel pack moistened with physiologic saline solution, and retracted both medially and ventrally by an assistant. The assistant must be instructed to distribute pressure on the displaced viscera evenly by using the flattened palms of his hands. The surgeon then places his left hand against the under surface of the liver and holds the liver firmly against the diaphragm. With his right hand he can then divide the membranous ligament between the right lobe of the liver and the vena cava and right kidney. While he continues to retract the liver upward the surgeon can then pass an aneurysm hook back through the avascular space behind the cava above its last abdominal tributary, the right lumbo-adrenal vein.

Next, the surgeon grasps an end of a strip of laminated cellophane tape with a cystic-duct forceps and passes it behind the cava, through the rent he has created in the avascular space. In the same manner, he passes the end of the band around the cava a second time. Finally, he draws the band tightly around the vessel and the tip of the cystic-duct forceps, which he has insinuated for the moment between the band and the wall of the cava, and ties it in this position with two accurately made square knots. The cystic-duct forceps is withdrawn, and the degree of constriction is noted. If the diameter has been reduced to not quite half the original diameter, which is the proper degree of constriction, the free ends of the tape are cut about ¼ inch (about 0.6 cm.) from the knot. If greater or lesser degrees of constriction have been produced, the band is removed and a new one is applied.

The assistant then changes his position slightly, exerting more traction on the first portion of the duodenum in a caudal direction. The gastrohepatic ligament is now put on tension and the surgeon can easily strip adjacent tissue from the short segment of portal vein, between the point where it receives its last tributary and the point where it divides into its hepatic branches. A second laminated cellophane band is placed and tied about the portal vein, in the same manner in which the band was placed on the vena cava.

It is of the greatest importance that trauma to the omentum, liver, and adjacent organs, particularly the duodenum, duodenal mesentery, and pancreas, be avoided. If one scrupulously avoids trauma and confines his dissection to the minimum required for placement of the bands, he will be rewarded by finding only a few delicate and avascular adhesions when hepatectomy is performed. In order to avoid adhesions in the area of the celiotomy incision we have closed the peritoneum with an everting suture of 000 chromic catgut.

Only very rarely does a dog not survive the first operation. Recovery is rapid, and no special care or diet is required. Body weight is maintained, and general condition remains good. Within a few weeks a number of large, full, tortuous, superficial veins running in the direction of the long axis of the body may be observed on the anterior abdominal wall. Although hepatectomy may be performed six to eight weeks after the first operation, we prefer to wait about four months, until the adhesions in the neighborhood of the liver have become less vascular.

Second Operation (Hepatectomy).—The removal of the liver is performed through a right thoracico-abdominal incision (Fig. 1, *B*), while the animal is under ether anesthesia administered by an insufflation machine. The dog is placed on its left side with a rest or pad under the lower part of its chest. A long incision is made in the plane of the tenth right intercostal space. After the intercostal muscles have been divided in a line equidistant from the tenth and eleventh ribs, the ribs are spread and held widely apart by a self-retaining retractor. Our retractor is a Balfour abdominal retractor converted for the purpose by a change in the blades; the blades are fenestrated, are shaped to fit around a rib, and are attached to the arms of the retractor by swivels. A large surgical sponge is usually an adequate pack to hold back the tip of the right lung. An incision in the diaphragm is begun where the intercostal incision crosses the inferior costal border and is extended, in the direction of the muscle

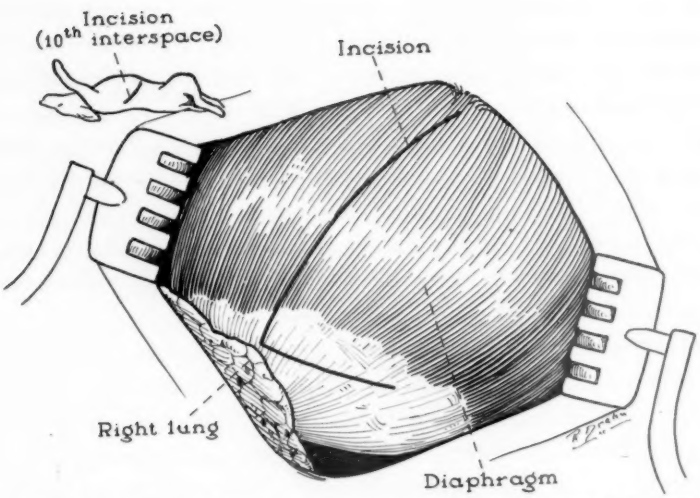

Fig. 1, *B*.—The incision used for hepatectomy. A self-retaining retractor is shown holding the right tenth and eleventh ribs widely apart, and the line of incision in the diaphragm is indicated.

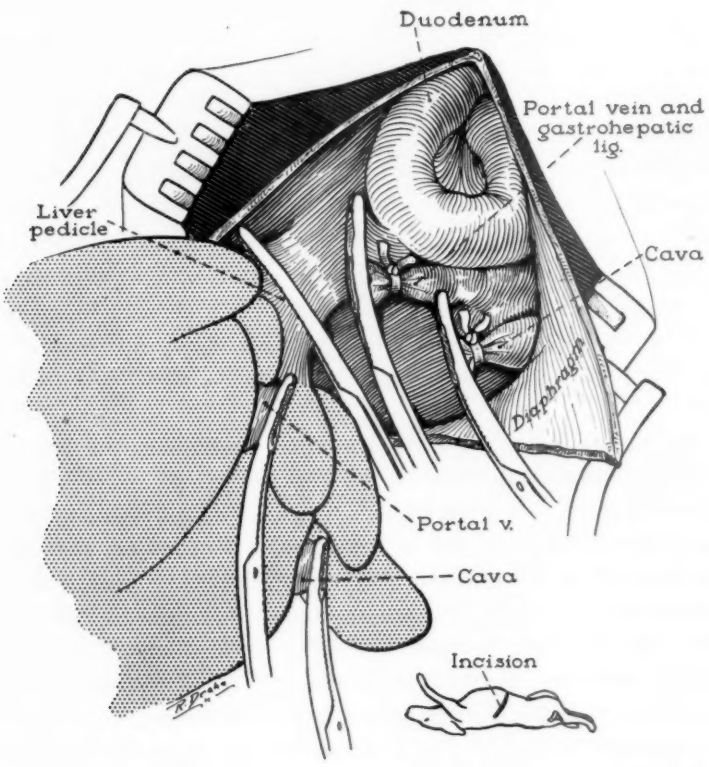

Fig. 1, *C*.—Removal of the liver. Heavy intestinal clamps are shown on the ends of the divided abdominal vena cava and structures in the free edge of the divided gastrohepatic ligament, and the first clamp has been placed on the vena cava between liver and diaphragm.

fibers, to a point in the tendon 1 cm. lateral to the foramen of the vena cava. Thence, the incision is continued laterally in such fashion that the tendon is divided in its long axis. Bleeding points on the edges of the diaphragm are ligated, and the anterolateral flap is turned outward. Most of the right surface of the liver and the duodenum will now be exposed.

The first step in removal of the liver is the freeing of adhesions between the upper part of the duodenum and its mesentery and the right inferior hepatic surface. These adhesions are always observed after the preliminary operation but are delicate when that operation has been performed properly. While the assistant exerts gentle traction on the duodenum, the surgeon may quickly and easily separate these organs by starting a plane of cleavage with a scalpel and continuing it with his finger. No attention is paid to the brisk ooze of blood from the hepatic surface, and the few bleeding points on the duodenal mesentery may be identified and ligated later.

In the next step the structures in the free edge of the lesser omentum, the common bile duct, hepatic artery and portal vein, are divided (Fig. 1, *C*). This may be done quickly, by inserting a finger through the epiploic foramen and by guiding one blade of an opened, heavy, curved, intestinal forceps over the finger. This forceps is placed close to the liver and closed tightly, and a second forceps is placed 1 cm. or more away, toward the duodenum. The structures in the free edge of the lesser omentum are then divided between the forceps, close to the one on the hepatic side.

Next, the left triangular ligament of the liver is divided. To do this the right hand must be placed beneath the left lobes and these lobes lifted as much as possible, in order to stretch the ligament and make it clearly visible. After the ligament has been cut it is quite easy to gather together all the tissue between the hilus of the liver and the lesser curvature of the stomach, the remainder of the lesser omentum, and to divide it between clamps.

The inferior vena cava is then divided (Fig. 1, *C*) between two clamps placed close to the inferior surface of the liver. The surgeon must keep as far above the right kidney and adrenal as possible in doing this, and should avoid manipulation of tissue caudal to where he places the clamps, tissue which contains greatly dilated veins of Retzius. Application of the clamps on the cava is facilitated by pushing the finger through the avascular tissue between it and the lower portion of the right crus of the diaphragm. One blade of each of the clamps may be inserted behind the cava through this aperture. After the cava has been divided between the clamps and while the assistant holds and lifts on the liver, the surgeon divides the right hepatodiaphragmatic ligament and the remaining areolar tissue behind the hepatic portion of the cava.

The last step in removal of the liver is division of the vena cava between liver and diaphragm. To do this, the cava is placed on stretch by traction on the liver, and a heavy intestinal forceps is placed so that when it is tightened it will crush the thin cuff of hepatic tissue about the cava (Fig. 1, *C*). This clamp is released and tightened several times in order to crush more hepatic tissue and thus to create a long enough segment of vena cava so that two heavy in-

testinal forceps may be applied between the liver and the diaphragm. After the surgeon has cut between the liver and the nearer clamp, the liver is free from all attachments and may be removed.

The vena cava is ligated below its diaphragmatic foramen by three heavy cotton or silk ligatures (Fig. 1, *D*). The first of these is passed on a needle through the diaphragmatic tissue adjacent to the cava under the first clamp. While this clamp is slowly released by the assistant, the ligature is tightened and tied. A second heavy ligature is tied under the remaining clamp. Before this clamp is removed the cuff of vena cava should be transfixed several times with another heavy ligature. Two heavy ligatures, the first of which is tightened while the intestinal clamp is released slowly and then reapplied, are required

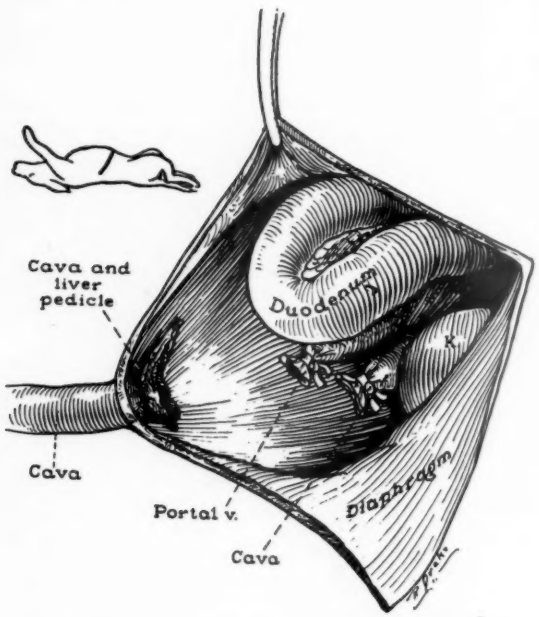

Fig. 1, *D*.—Completion of hepatectomy. Ligatures are shown on the end of the vena cava and on the gastrohepatic ligament. K. is kidney.

for the mass ligations of the structures contained in the free edge of the gastrohepatic omentum (Fig. 1, *D*). Single heavy ligatures are sufficient to ligate the remainder of the omentum and the abdominal vena cava (Fig. 1, *D*). Just behind the ligatures placed on the cava and on the tissue containing the portal vein the cellophane bands which were placed on these vessels earlier will be seen, embedded in dense fibrous tissue. Bleeding points are now searched for and ligated with great care. Extreme gentleness must be used in the handling of tissue to expose the areas where bleeding is most likely to occur, namely, the upper pole of the right kidney, duodenal mesentery, lesser curvature of the stomach, and the diaphragm near the foramen of the vena cava.

During closure of the diaphragm and chest the surgeon should bear in mind that the liverless dog is disposed to bleed. Not only is it unable to form more prothrombin, but there is a tendency after a few hours for capillaries to

leak. It is imperative, therefore, that all actively bleeding points be ligated and that the edges of wounds, especially of the diaphragm, be approximated with continuous, hemostatic sutures.

The lungs must be expanded when the thoracotomy incision is closed.

COMMENT

Our experience with this method of hepatectomy is that it gives about the same results as the three-stage method, in which a reverse Eck fistula is made followed by ligation of the portal vein before hepatectomy. That is, the dogs are in good condition after operation and tend to live about the same length of time before they succumb in coma. If both the preliminary operation and hepatectomy have been performed properly, there will be no venous congestion of the viscera or hind legs and very little loss of blood into the abdominal and pleural cavities. It does not appear that removal of the liver through the thoracicoabdominal incision is more disturbing to the dog than when removal is performed through the abdomen.

The advantages of this method over the older one are that the step of making a portacaval anastomosis is eliminated, that only one preliminary operation is required, and that exposure of the liver for hepatectomy is not only excellent but is away from the region of adhesions which may have been produced by the preliminary operation. Thus, time and effort are saved and the securing of the vena cava in the foramen of the diaphragm and of adjacent bleeding areas is facilitated.

One snag in this and in all methods of hepatectomy is that, once the blood supply of the liver is clamped off, the dog is in a physiologic sense without a liver. For this reason ether, which can be expelled through the lungs, is the anesthetic agent of choice. For this reason also, deep and long anesthesia is to be avoided. The best results will be obtained if hepatectomy is performed in less than an hour, and if administration of ether is stopped at a time early enough for the dog to commence to respond during the closure of the skin.

It might be wondered why the vena cava is not ligated just above the diaphragm, as well as below. To do this seems not only unnecessary but probably, because it would very likely interfere with drainage of veins in the central portion of the diaphragm, harmful.

SUMMARY

We have found a two-stage method of hepatectomy to be satisfactory for studies on the liverless dog. The first operation is performed through the abdomen and consists in placing laminated cellophane tapes around the portal vein and the vena cava close to the liver. The tapes are tied tightly enough to cause moderate constriction of the vessels, but in the course of the next six to eight weeks they produce fibrous strictures which almost completely occlude the portal vein and the vena cava. Collateral veins, which by-pass the liver, enlarge as the degree of obstruction increases and, by the time obstruction is maximal, these veins are the channels through which virtually all portal and inferior caval blood reaches the heart. The liver of such a dog, however, appears to be

normal, and health and weight of the dog are maintained indefinitely. The second operation, hepatectomy, may be performed at any time after obstruction of the cava and portal vein is established. Surgical exposure for hepatectomy is obtained through an incision in the tenth right intercostal space and an L-shaped incision in the diaphragm. The principal advantage of this thoracico-abdominal incision is that it facilitates division and ligation of the vena cava above the liver, just below its foramen in the diaphragm.

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GASTRIC LIPOMA

DONALD H. BADNER, M.D.,* AND MAX CAPLAN, M.D.,** MERIDEN, CONN.

THE diagnosis of rare lesions has always been a challenge, particularly when no definite symptom complex has been established for the particular lesion. This is true for the most uncommon of benign tumors of the stomach, namely, lipoma of the stomach. It is because of the similarity in symptomatology and x-ray findings to early gastric carcinoma that we are presenting this very interesting case of a submucous gastric lipoma. In our hospital, this is the first case on record.

CASE REPORT

S. L., a 56-year-old white man, complained of "stomach trouble" for about two years. This was manifested by belching, sour taste in the mouth, and bloating of the epigastrium. He used milk of magnesia tablets which gave him relief. For several weeks before his admission to the hospital, he began to experience acute postprandial epigastric pain which lasted for ten to fifteen minutes and then left him with a residual soreness in the epigastrium. His appetite became poor; he began to feel weak and tired; he lost about ten pounds.

Physical examination was essentially normal. Laboratory data included: red blood count—5.16 million, hemoglobin—14.6 Gm., white blood count—6,150, urine—normal, total proteins—6.81, albumen—4.99, globulin—1.72, prothrombin time 100 per cent. A cholecystogram revealed a normal gall bladder. A gastrointestinal series revealed a filling defect in the prepyloric region of the stomach. There appeared to be a rigidity to the lesser curvature of the stomach overlying the filling defect. Our diagnosis was gastric polyp, and, because of the suggestive fixation of the gastric wall, we considered the possibility of carcinoma.

The patient was admitted to Meriden Hospital, and on Feb. 7, 1951, operation was performed. In the prepyloric region of the stomach, a rubbery mass, about 3½ by 1½ by 1 cm., was palpated in the anterior wall. A gastrotomy was performed and a well-encapsulated lipoma was seen submucosally, protruding through the gastrotomy incision. The lipoma bulged into the lumen of the stomach and the mucosa overlying the lipoma, as well as the rest of the stomach, was entirely normal. The liver appeared normal and no lymph nodes could be felt or seen. The lipoma was easily removed, and the gastrotomy incision was closed. The patient made an uneventful recovery and was discharged from the hospital symptom free, on Feb. 16, 1951.

Pathologic Report.—Specimen consisted of a smooth encapsulated lipoma measuring 3 by 1½ by 1 cm. On section, no unusual features were noted. Fat resembled adult fat in type. Microscopic sections showed adult fat cells.

INCIDENCE

Although gastric lipoma is still a very rare lesion, the reported incidence has been steadily increasing, mainly because the increased awareness of, and interest in, early diagnosis of gastric carcinoma have led to more frequent and more numerous x-ray examinations. Like other benign tumors of the stomach,

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*Junior Attending Surgeon, Surgical Service, Meriden Hospital.
**Chief, Medical Service, Meriden Hospital.

lipomas, in the majority of cases, are asymptomatic so that they may not be recognized. The incidence of gastric lipoma, therefore, is, at best, underestimated.

In 1925, Eliason and Wright[6] compiled a list from the literature of 610 benign stomach tumors and found that lipomas comprised 4.8 per cent of them. These same authors found one gastric lipoma in 8,000 autopsies. Comfort,[4] in 1931, reported four cases of gastric lipoma in 3,924 autopsies. In 1936, Minnes and Geschickter[8] analyzed 931 reported cases of benign gastric lesions, of which there were 32 lipomas, or 3.4 per cent. An excellent review of the literature

Fig. 1.—Filling defect in prepyloric region of stomach with suggestive rigidity of wall along lesser curvature overlying the defect.

from 1835 to 1940 by Rumold,[11] in 1941, revealed 33 reported cases of submucous gastric lipoma, seventeen of which were found at necropsy and sixteen at operation. In 1946, Scott and Brunschwig[12] collected five more cases from the literature since 1941 and added one case of their own. Hobbs and Cohen[7] reported their interesting case of gastric lipoma with intussusception in 1941. In 1948, Alvarez, Lastra, and Leon[1] collected four more cases from the literature since the report of Scott and Brunschwig[12] and described a case of theirs, bringing the total to forty-four. In 1949, Palazzo[10] reported six cases from the files and pathologic reports at the Massachusetts General Hospital since 1900. Since

1949, reports by Thompson and Oyster,[13] Culver and Dobrak,[5] and Warren and Brandenburg[14] have brought the total to fifty-four. Our case represents the fifty-fifth reported case.

ETIOLOGY

The origin of lipomas and other benign tumors of the stomach is unknown. However, it is believed by some that they arise from a primitive anlage separated during fetal life. Although this theory is highly speculative, it is used to explain those cases which are familial in character. The other popular theory is that of chronic irritation which results in low-grade inflammation and hypertrophy. This theory, however, is not substantiated in the majority of cases, because microscopic examination does not reveal any evidence of inflammation and in cases of chronic gastritis, no evidence of metaplasia is seen.

Fig. 2.—Photograph of excised lipoma.

PATHOLOGY

A lipoma of the stomach is no different than a lipoma found in other locations. Grossly, it is a characteristic, encapsulated, fatty tumor either round, ovoid, or lobulated. It has been reported that lipomas of the stomach may range in size from a few millimeters to 9 and 10 cm. in diameter. They may be single or multiple, sessile or pedunculated. Although they occur in any part of the stomach, they occur more frequently in the subserous layer, in which case they project outward. When they are submucous in location, they protrude into the lumen of the stomach and may cause erosions and ulcerations of the mucosa with bleeding. Submucosal pedunculated lipomas are those which produce pyloric obstruction or intussusception.

SYMPTOMS

The symptomatology of gastric lipoma follows no definite pattern. Bockus[2] and Comfort[4] state that the majority of all benign tumors are never discovered inasmuch as they are too small to produce symptoms. Thompson and Oyster,[13] in their series of benign tumors of the stomach, estimated that only one-third produced symptoms, the others being incidental findings at autopsy. Of the six cases of gastric lipoma reported by Palazzo,[10] all were asymptomatic. The multiplicity of symptoms that can be produced depends upon the location, size, and complications. Benign tumors notoriously cause bleeding as a result of ulceration of the mucosa, thus producing symptoms of weakness, anemia, fatigue, hematemesis, melena, and weight loss. Sometimes massive hemorrhages may occur, as in the case reported by Cattell.[3] Pain may or may not be present and if it is, it is usually in the epigastrium or periumbilical region. If the tumor is located near the cardia, dysphagia is the chief complaint. Pyloric lesions, particularly if they protrude into the lumen, will produce symptoms of periodic or complete obstruction. A pedunculated tumor may also produce an intussusception as illustrated so well by the case of Hobbs and Cohen.[7] These authors state that intussusception of a tumor into the duodenum may simulate gall bladder disease with jaundice, because the tumor may block the papilla of Vater. It is quite obvious that this lesion may simulate gastric carcinoma and that it may coexist with carcinoma as reported by Scott and Brunschwig.[12] Our own case is one of vague digestive complaints associated with weight loss and weakness, which suggested to us the possibility of early gastric carcinoma.

DIAGNOSIS

In most cases, physical examination is of no help. If the tumor is large enough, it may be palpated, but that is not characteristic. The most significant step toward diagnosis is x-ray examination. In 1924, Moore[9] established the following criteria for roentgen recognition of benign tumors of the stomach, and stated that if these signs are not characteristic they are at least suggestive.

1. Filling defect that is circumscribed and punched out in appearance.
2. Filling defect usually on gastric walls, leaving the curvatures regular and pliant.
3. Rugae in the immediate area of the tumor are obliterated as in inflammatory of malignant lesions, but elsewhere they are more nearly normal in their arrangement and distribution.
4. Little or no disturbance in peristalsis and retention is uncommon except when lesion is at or near the pylorus.
5. Absence of a niche, incisura, or other evidence of spasm.
6. Rarely a tumor sufficiently large to be palpated.
7. Close and complete approximation of the walls of the barium-filled stomach.

In 1950, Culver and Dobrak[5] suggested that a "moveable tumor extending into the lumen of the gastro-intestinal tract without a demonstrable pedicle"

on x-ray examination is the point of differentiation between a submucosal lipoma and a pedunculated polyp.

In addition to a history, physical examination, and x-ray, a procedure which has become very important in the past few years is gastroscopy. In competent hands, gastroscopy is a relatively simple and not unpleasant procedure which can aid tremendously in diagnosis, especially in differentiating between a benign and a malignant lesion. It may be difficult, however, to differentiate between benign lesions, especially those which are nonepithelial in origin.

TREATMENT

It is generally agreed that surgical treatment is the treatment of choice. In uncomplicated tumors, local excision of the tumor may be all that is necessary. It is believed by some that excision of the tumor with the surrounding stomach wall is indicated, mainly because the tumor may not be grossly recognized at operation, and also because of some reported instances of recurrence where only the tumor was excised. Where complications such as hemorrhage, ulceration, or intussusception occur, it has been reported that sleeve resections and subtotal gastric resections have been performed.

DISCUSSION

The diagnosis of gastric lipoma is a difficult one. Because the symptomatology of lipoma is so variable, it is difficult to differentiate this tumor from other benign tumors and in some cases from malignant lesions of the stomach. X-ray and gastroscopic findings are very suggestive but not conclusive. The case reported here is one of vague digestive complaints associated with weakness and weight loss, and an x-ray which suggested to us gastric carcinoma. A local excision of the tumor was performed, because it was recognized by gastrotomy and the encapsulated lipoma could be easily removed, just as it is elsewhere on the body.

SUMMARY

A review of the literature of gastric lipoma has been presented along with an interesting case study of a submucous gastric lipoma. X-ray findings were those of a gastric polyp with suggestive findings of gastric carcinoma. This case is the fifty-fifth case of gastric lipoma reported in the literature.

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Case Reports

ANEURYSM OF THE HEPATIC ARTERY

Report of a Case Treated by Wiring

Richard W. Dwight, M.D.,* and John W. Ratcliffe, M.D.,**
Framingham, Mass.

(From the Surgical Service, Cushing Veterans Administration Hospital)

NINETY-ONE cases of aneurysm of the hepatic artery have been reported in the literature, in twenty-eight of which operations were done, but in only one was the aneurysm seen and treated successfully. The patient reported here had an extrahepatic aneurysm, which was known to have been present for two years, and which was treated by wiring.

E. J. McN. (CVAH27283), a 57-year-old forester, was admitted to Cushing Veterans Administration Hospital in December, 1947, complaining of weakness and the passage of black stools which had occurred eight weeks before, and again just before admission.

The past history included malaria in childhood, a perforated appendix at the age of 17 years, an abscess in the region of the left kidney, treated by surgical drainage at the age of 34 years, and a fall, resulting in fracture of a lumbar vertebra, at the age of 48 years.

Physical examination was negative except for the blood pressure, which was 156/102, mild hypertensive retinopathy, and operative scars in the left flank, and right lower quadrant.

The hemoglobin was 14 Gm. per 100 ml., and the Kahn blood test was negative. Other laboratory findings were within normal limits. X-ray examination revealed wedging of the body of the second lumbar vertebra. Barium studies of the entire gastrointestinal tract at that time, and again two months later failed to reveal a cause for the passage of black stools.

One year later the patient had two attacks of faintness followed by the passage of bloody and tarry stools. Examination and laboratory studies were unchanged except that the hemoglobin was 10.2 Gm. per 100 ml., the stools were positive to a guaiac test, and a polyp, 15 cm. above the anus, was seen on sigmoidoscopy.

At operation in December, 1948, a pulsatile mass, approximately 4 by 5 cm., was felt on the under surface of the liver. There was a thrill in the hepatic artery proximal and distal to the mass, which was believed to be an aneurysm of the hepatic artery. The polyp, which was removed through a longitudinal incision in the sigmoid, was 1 cm. in diameter, on a stalk 1 cm. long, and microscopically appeared benign. No other polyps were palpated in the large bowel.

The patient was well for two years, until in October, 1950, he began to have mild heartburn in the evening. On November 9, he felt restless, suddenly became weak, and passed an estimated pint of liquid red blood by rectum.

The blood pressure was 138/90, pulse 100, hemoglobin 8.8 Gm. per 100 ml. and hematocrit 31 per cent. Material from the rectum, and coffee-ground material obtained from the stomach by tube, both gave a strongly positive guaiac test.

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*Assistant Chief, Surgical Service, Cushing Veterans Administration Hospital.

**Senior Resident, Surgical Service, Cushing Veterans Administration Hospital.

Other laboratory examinations, including various liver function tests, x-ray examinations, sigmoidoscopy and gastroscopy were noncontributory. Retrograde aortography[12] failed to demonstrate the hepatic artery.

Laparotomy was performed on Dec. 8, 1950. A pulsating mass 5 by 6 cm. was felt cephalad to, partly behind, and adherent to the pylorus and first part of the duodenum. With a finger in the foramen of Winslow a short length of hepatic artery was felt between the mass and the hilum of the liver. The stomach and duodenum were otherwise normal to palpation and inspection. The entire small bowel, cecum, and transverse colon were inspected and palpated, and the rest of the large bowel was palpated without revealing any abnormality. The liver and gall bladder appeared normal. The spleen and kidneys felt normal.

The celiac axis was exposed at the junction of the splenic and hepatic arteries. The hepatic artery was 5 mm. in diameter. Digital compression of the artery stopped pulsation in the aneurysm. As a precautionary measure a heavy silk ligature was passed around the artery but not tied. With the posterior peritoneum opened, the aneurysm was seen to have a smooth shining wall (Fig. 1).

Fig. 1.—Aneurysm of the hepatic artery as seen at operation. The aneurysm is at the tip of the forceps.

A Blakemore needle was inserted into the aneurysm, and .009 stainless steel wire, which had been previously roughened with emery cloth, was pumped in until the aneurysm would hold no more. A few more feet of wire were inserted at a different point. In all, 31 feet of wire were used. Both times removal of the needle was followed by brisk hemorrhage, which ceased in a few minutes when the wire was cut off, and Gelfoam soaked in thrombin held with pressure over the puncture site. The mass of wire could be felt through the walls of the aneurysm, which, however, still continued to pulsate. The ligature was removed from the hepatic artery, and the abdomen closed in layers.

Recovery was uneventful. A stereoscopic x-ray showed a roughly cylindrical mass of wire, 5 cm. in diameter in the right side of the abdomen. A gastrointestinal series one month after operation showed slight narrowing of the distal portion of the duodenal bulb, in association with the mass of wire, but six months later no narrowing was seen. The

patient was discharged on the tenth postoperative day, returned to work in two months, and was well until Sept. 1, 1951, when he passed two small tarry stools on successive days. He felt no weakness or faintness. Hemoglobin was 10.7 Gm. per 100 ml. Physical examination, x-rays, and sigmoidoscopy were all negative. After two days the stools were guaiac negative, and there was no further evidence of bleeding. The patient was discharged on the seventh day. Tarry stools were observed once in October and once in December. He was again studied, but no cause was found. He was seen Jan. 24, 1952, and was symptom free.

Fig. 2.—Postoperative x-ray showing wire in the aneurysm.

DISCUSSION

Friedenwald and Tannenbaum, [10] in 1923, presented a comprehensive review of 65 cases of aneurysm of the hepatic artery. Malloy and Jason[25] added 20 cases, and there have been 5 cases subsequently reported[13, 14, 24, 41] as well as an earlier case[9] not previously included.

From the data in these reports it appears that in 89* instances of aneurysm a severe systemic infection, such as pneumonia, empyema, or typhoid fever, had

*One case has been excluded because of duplication, and one because of uncertainty in diagnosis.

occurred previously in 33 patients, arteriosclerosis was present in 18, syphilis in 7, and cholelithiasis in 6. Trauma in the region of the liver had occurred in 7. There was no determinable etiology in the remaining cases. Three-fourths of the aneurysms were extrahepatic, the rest intrahepatic, except for three patients in whom both types were present.

Seventeen aneurysms were found unruptured, either at operation or postmortem examination, in one case there is doubt, and in 71 perforation had occurred. Thirty aneurysms ruptured into the peritoneal cavity, 29 into the gall bladder or bile passages, 5 into stomach or duodenum, 1 into the portal vein, and 5 into the peritoneal cavity and one of the other sites.

In the 74 reports in which a history was given the chief signs and symptoms were pain in 52, jaundice in 38, and gastrointestinal hemorrhage in 43. All three manifestations were present in 24 instances. The pain was located in the right upper quadrant and varied from slight discomfort to severe steady or colicky pain. The hemorrhage took the form of hematemesis, melena, or both, and varied from occult blood in the stools to massive blood loss. The duration of symptoms was from a few hours to two years, in a few cases collapse from rupture of the aneurysm into the peritoneal cavity being the first sign.

In the case reported here it is impossible to say whether the melena occurring in 1947 and 1948 was due to the aneurysm or the polyp. That the hemorrhage in 1950 was due to the aneurysm is suggested by the presence of blood in the stomach, and by the fact that complete study and exploration failed to reveal any other cause. The portion of the duodenum lying against the aneurysm was the only part of the upper gastrointestinal tract that could not be satisfactorily inspected and palpated. If this was the site of the bleeding either of two explanations are possible: (1) ulceration of the duodenum due to pressure from the aneurysm, with or without actual rupture of the latter, (2) duodenal ulcer unrelated to the aneurysm. The absence of symptoms other than slight heartburn for a few weeks, and the negative x-ray findings make the latter seem unlikely.

There are reports on 28 patients who were operated upon. Thirteen of these were in Friedenwald's series, the rest have not previously been summarized together. In Merkel's* case, the aneurysm was unrelated to the operation or death. In Friedman's case the operation was exploratory, and the diagnosis uncertain. Twenty-two of the remaining twenty-six patients died, twelve of them with the diagnosis still unrecognized. In one[24] only an exploration was done. In four[7, 16, 27, 37] posterior gastroenterostomy was performed in the belief that bleeding was due to an ulcer. In 7 surgery was directed to the gall bladder,[4, 5, 15, 21, 28, 39, 41] cholecystotomy, or cholecystectomy, with or without choledochostomy being performed, although in two of them the diagnosis of aneurysm was made at operation. The immediate cause of death cannot be determined in many of the reports. "Collapse," "exhaustion," and "heart failure" were given as the causes in many of the deaths that occurred within a few days of operation; repeated hemorrhage or liver failure were the principal

*Cited by Friendenwald.[10]

causes in the patients who lived for a week or more. In one case[42] a ruptured intrahepatic aneurysm was found at operation, the patient dying before anything could be done, while in six[2, 10*, 14, 21, 34] the aneurysm was entered surgically. The ensuing hemorrhage was controlled with tamponade, suturing, or both. Tamponade produced thrombosis of the artery and liver necrosis in one case, there was death from repeated hemorrhage in another, and early death (1 to 5 days postoperative) from unspecified causes in the rest. In the remaining 3 fatal cases ligation of the hepatic artery caused death from liver failure in 2[38, 40] and aneurysmorrhaphy was followed by death from uremia and sepsis in one.[13]

In 3 of the successful cases intrahepatic aneurysms were assumed to be the cause of hemorrhage, but were not seen at operation. In Käding's [17] and Colmers'[8] cases hematemesis and melena occurred several months after direct trauma, in one there was jaundice, in the other clots in the gall bladder, and both patients were cured by ligation of the hepatic artery. Anderson's[3] patient, who had syphilis and had been previously treated for aneurysm of the radial artery, was operated on as an emergency. Bleeding from the right lobe of the liver was controlled by "two mattress sutures and a gauze pack."

In 1903 Hans Kehr[18] operated on a 29-year-old man who developed pain, jaundice, and hematemesis following empyema. He found an extrahepatic aneurysm, ligated the artery, packed the sac, and sewed the right lobe of the liver in the wound. A 2 cm. strip of liver margin became necrotic and was trimmed off on the nineteenth day. Following this the wound healed, and the patient was still in good health 6 years later.

It is evident that operative treatment of hepatic aneurysm has been largely unsuccessful. A diagnosis of intrahepatic aneurysm can only be made from inference (a positive diagnosis might be made by hepatic arteriogram at operation). If we accept Colmers' and Käding's cases, ligation of the hepatic artery has cured three cases of aneurysm, and failed in two. Grant and associates[14] have suggested that massive doses of antibiotics might lower the mortality of ligation, as Markowitz has demonstrated in dogs. Implantation of the proximal end of the hepatic artery into the portal vein, successful in preventing liver necrosis in dogs, would almost certainly produce the complications of portal hypertension, as illustrated by Sachs'[33] case where rupture of an aneurysm into the portal vein was followed by fatal hemorrhage from an esophageal varix.

Reconstruction of the artery, either by excision of the aneurysm, and end-to-end anastomosis, or by aneurysmorrhaphy would theoretically be the ideal procedure, if the situation made it technically possible.

The method of wiring aneurysms, first described by Moore in 1864, was employed by Blakemore and King[6] in 1938, using enameled wire, which they heated electrically to 80° C. Linton[22] has had equal success using fine, stainless steel wire roughened by emery cloth, as described. In the case presented here more radical methods may still be tried if it becomes certain that the aneurysm is causing hemorrhage.

*Niewerth, cited by Friedenwald.

SUMMARY AND CONCLUSIONS

Although aneurysm of the hepatic artery is rare, it should be considered in the presence of otherwise unexplained upper abdominal pain, jaundice, and gastrointestinal hemorrhage.

Twenty-eight patients with aneurysms have been operated on with fatal results in all of them in whom the diagnosis was not made at operation. Ligation of the hepatic artery produced the only reported cures but was not uniformly successful.

An additional case is reported in which the aneurysm was treated by wiring.

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LEIOMYOSARCOMA OF THE DUODENUM WITH GASTROINTESTINAL HEMORRHAGE

Report of a Case and Review of the Literature

William B. Ayers, M.D.,* and George A. Cunningham, M.D.,**
New Orleans, La.

THE successful resection of a rare duodenal tumor in an elderly woman stimulated presentation of this case and review of the literature.

CASE REPORT

E. P., an unmarried woman, 80 years old, was admitted to Foundation Hospital, Dec. 21, 1950, because of intermittent bleeding from the gastrointestinal tract of five months' duration. Three years prior to admission she first began to experience a burning sensation in the region of the lower end of the sternum associated with acid eructation. This usually occurred at night, particularly if she had eaten greasy foods in the evening, and was always relieved by taking sodium bicarbonate. Nine months prior to admission she noted that coarse foods seemed to "stick" in the region of the lower end of the sternum. This sensation was relieved by forced vomiting. For six months she had suffered from progressive weakness. Five months before admission, after vomiting a small amount of bright red blood, she lapsed into a shocklike state which necessitated hospitalization. Her stools were tarry in character and her hemoglobin was 30 per cent of normal. She responded favorably to three whole blood transfusions. Roentgenographic examination of the upper gastrointestinal tract revealed a "diaphragmatic hernia" but no other abnormality. On a regimen consisting of a bland diet with regular administration of antacids, the substernal burning was relieved. However, on three occasions since the initial episode, the patient was hospitalized because of weakness associated with the passage of tarry stools. Each time blood transfusions were administered for correction of the hemoglobin deficit. The last episode occurred three days before she was admitted to Foundation Hospital, at which time she received 500 c.c. of whole blood.

A cholecystogram performed several years previously had revealed stones in the gall bladder. Thirty years before, the patient had had a "tumor" removed from her abdomen.

Physical examination on admission revealed an obese, pale, senile, white woman who appeared chronically ill. The blood pressure was 150 mm. Hg systolic and 80 mm. Hg diastolic, and the pulse rate was 70 beats per minute. There was moderate sclerosis of the retinal arterioles and peripheral arteries. A systolic murmur was noted over the aortic area. Abdominal examination disclosed slight tenderness in the right subcostal area.

Initial laboratory studies revealed a red blood count of 2,430,000 per cu. mm., hemoglobin 7.6 Gm. per 100 c.c. and hematocrit 26 per cent. The white blood count and differential count were normal. The sedimentation rate was 25 mm. per hour and the prothrombin time 77.6 per cent of normal, bleeding time (Duke) 1 minute, 40 seconds, clotting time (capillary tube) 2 minutes, 25 seconds. Urinalysis yielded negative results. Blood urea nitrogen was 17 mg. per 100 c.c., fasting blood sugar 126 mg. per 100 c.c., serum bilirubin, direct 0.13 mg. per 100 c.c., and total 1.15 mg. per 100 c.c. Kahn and Wassermann reactions were negative. The benzidine test showed four plus occult blood in the stool; no ova or parasites were found. An electrocardiogram showed no abnormality and a roentgenogram of the chest revealed mild torsion of the aorta.

The patient received 2,500 c.c. of whole blood during the first 4 days of hospitalization, following which the hemoglobin had risen to 12.3 Gm. per 100 c.c. and the hematocrit to 40

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*Formerly Staff Member, Department of Surgery, Ochsner Clinic.
**Fellow in Surgery, Alton Ochsner Medical Foundation.

per cent. A hiatus hernia of the esophageal type was visualized by roentgenographic examination of the upper gastrointestinal tract, performed the second day after admission, the cardioesophageal junction being located 4 cm. above the hiatus. Films taken at the end of two hours demonstrated a small, round, filling defect in the lower ileum believed to be fecal material although the possibility of a gallstone was considered. Examination after the administration of a barium enema disclosed diverticulosis of the sigmoid colon. Gastric analysis revealed 23° free hydrochloric acid and 29° total acid before, and 58° free and 63° total acid after, administration of 0.5 mg. of histamine. Two subsequent upper gastrointestinal series performed Dec. 28 and Dec. 30, 1950, showed that the duodenal bulb was posterior in position, making it difficult to visualize. Multiple calcified stones were seen in the gall bladder, which was in close apposition to the descending portion of the duodenum. The previously reported hiatus hernia was confirmed but nothing additional was visualized. Esophagoscopy, performed Jan. 2, 1951, demonstrated that the cardia was located 30 cm. from the teeth and, except for pallor, the esophageal and gastric mucosa were normal throughout.

On the basis of the foregoing studies, the following diagnoses were entertained: (1) gastric ulceration in the hiatus hernia, (2) diffuse gastric hyperemia with bleeding, (3) cholecystojejunal fistula due to erosion of a gallstone, and (4) neoplasm of the duodenum, gastric cardia, or small intestine not visualized roentgenographically.

On Jan. 3, 1951, the red blood count had fallen to 3,170,000 mm. per 100 c.c., hemoglobin 9.1 Gm. per 100 c.c. and hematocrit 30 per cent. The patient received 1,000 c.c. of whole blood on this day and the following day, after which the hemoglobin was reported 13.9 Gm. per 100 c.c. and the hematocrit 42.5 per cent.

At exploratory laparotomy on Jan. 5, 1951, a tumor 3 cm. in diameter on the medial wall of the second portion of the duodenum extending into the head of the pancreas was resected and end-to-end anastomosis accomplished. There was no evidence of metastasis within the peritoneal cavity. The distal line of resection was located approximately 0.5 to 1 cm. from the papilla of Vater and a free flow of bile from the papilla was noted following the resection. Numerous stones were removed from the gall bladder and a cholecystostomy was performed. No stones could be palpated in the common duct. Because the tumor had to be dissected away from the head of the pancreas, development of a pancreatic fistula was anticipated; therefore, two drains were placed down to the region of the anastomosis.

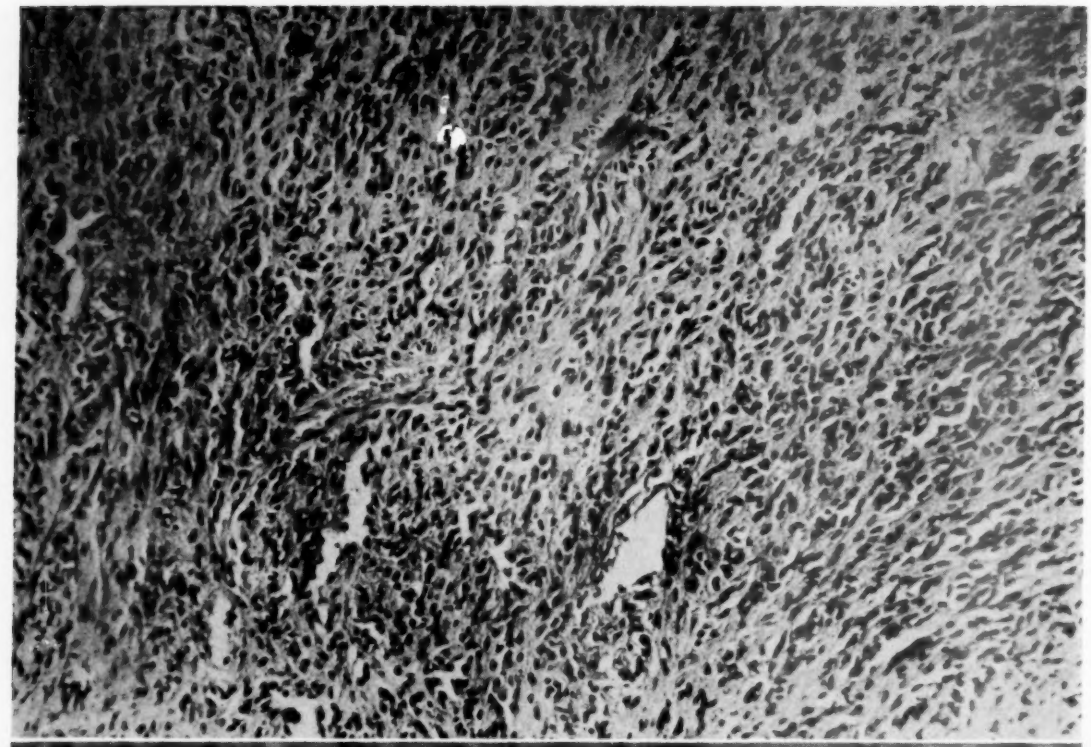
The specimen consisted of a segment of duodenum 6 cm. in length to which was attached a 3 cm., firm, encapsulated, slightly lobulated tumor. This tumor extended through all layers of the wall of the duodenum and on the mucosal surface there was an irregular area of ulceration 1.5 cm. in diameter. On cut section, the tumor was seen to be lobulated and grayish white in color with dark red streaks of old blood radiating throughout. The microscopic diagnosis was leiomyosarcoma of the duodenum.

The postoperative course was marked by two complications, which created a problem in fluid and electrolyte maintenance. A pancreatic fistula developed with profuse outpouring of pancreatic secretions and digestion of the surrounding subcutaneous fat. Also, after removal of the Levine tube on the fourth postoperative day, the patient experienced a severe substernal burning sensation on attempting to swallow. This dysphagia persisted for eleven days in spite of the administration of antispasmodics, alkalis, and olive oil, and restricted the patient's daily oral intake to from 60 c.c. to 420 c.c.

Fluid and electrolyte loss were adequately replaced parenterally. On the thirteenth postoperative day, fluoroscopic examination of the esophagus, following the administration of barium, revealed spasm and hyperperistalsis of the lower end of the esophagus, confirming the clinical impression of peptic esophagitis secondary to the hiatus hernia. Forty-eight hours later, the associated dysphagia subsided so that an adequate oral intake could be resumed.

By the time of discharge on the twenty-second postoperative day, the pancreatic fistula had closed, the wound was filling in with healthy granulation tissue, and drainage from the cholecystostomy tube was minimal. At the end of three months postoperatively, the patient had resumed normal activity. An upper gastrointestinal series at that time revealed the

Fig. 1.



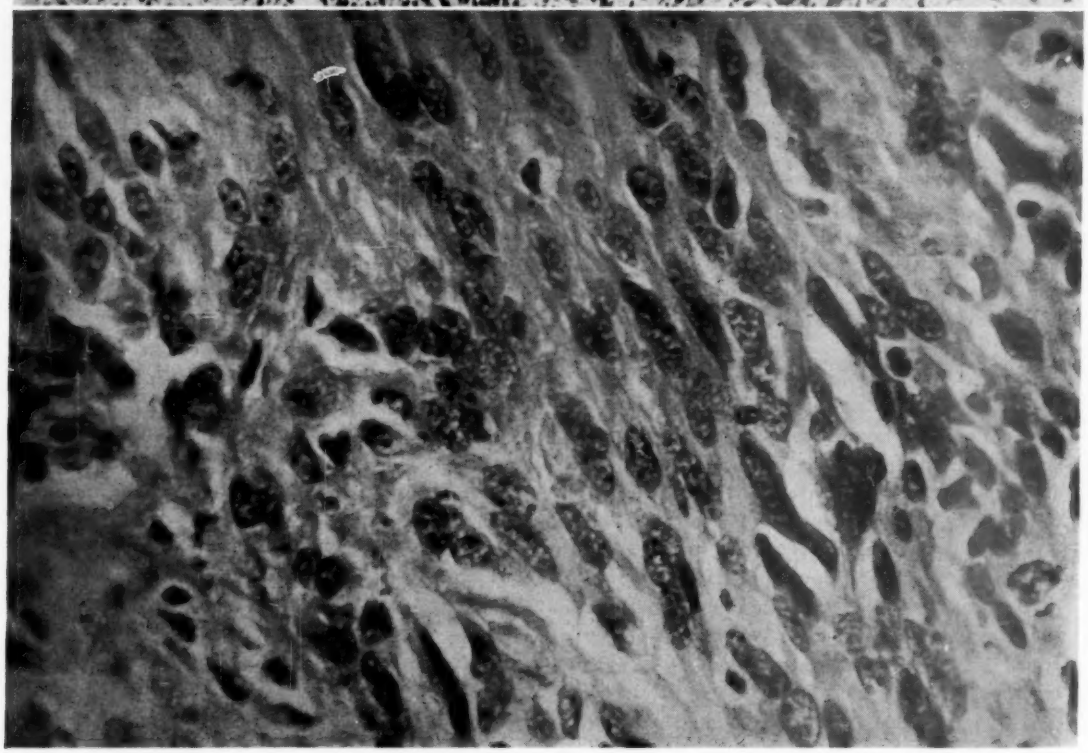


Fig. 2.

Fig. 1.—Primary leiomyosarcoma of duodenum (Case E. P.). (×100.)

Fig. 2.—High-power magnification of same tumor showing elongated and ovoid cells with large vesicular nuclei. (×400.)

hiatus hernia to be unchanged, but there was no evidence of esophagitis. The stomach and duodenum appeared normal and there was no obstruction at the anastomotic site. At the present writing, 9 months postoperatively, the patient remains active and asymptomatic.

REVIEW OF LITERATURE

Since the first reported case of leiomyosarcoma of the duodenum by Von Salis[1] in 1920, 16 cases have appeared in the literature (Table I); the present case, therefore, represents the seventeenth. The case reported by Shackelford and co-workers[17] is not included in this total because it could not be established definitely whether the duodenal tumor was secondary to a leiomyosarcoma of the uterus removed four and one-half years previously or was a second primary lesion. The case described by Nitshe and Suckle[13] as a leiomyosarcoma of the "ampulla of Vater" has been included in the total figure of 17 because the microscopic description indicates that the tumor arose from the muscular layers of the duodenum.

TABLE I. CASES OF LEIOMYOSARCOMA OF DUODENUM REPORTED IN LITERATURE

AUTHOR	CASES
Von Salis[1] (1920)	1
Brdiczka[2] (1931)	1
Andersen and Doob[3] (1933)	1
Silverstone[4] (1934)	1
Seymour and Gould[5] (1936)	1
Foshee and McBride[6] (1939)	1
Itikama[7] (1940)	1
Harrington and Ganshorn[8] (1940)	1
Mayo[9] (1940)	1
Henning and Garland[10] (1941)	1
Williams[11] (1944)	1
McCullough[12] (1944)	1
Nitshe and Suckle[13] (1947)	1
McLean[14] (1948)	1
Heymann and Clark[15] (1950)	1
Swartz and Eckman[16] (1951)	1
Ayers and Cunningham (1951)	1
Total	17

Although the total number of cases is small, analysis of the individual case reports does permit presentation of certain observations. Of the 17 cases, adequate information is lacking regarding the clinical course and detailed pathologic findings for those reported by Itikawa[7] and Mayo.[9] One of the two cases reported by Mayo, in his review of malignancies of the small intestine occurring at the Mayo Clinic between 1907 and 1939, had previously been described in detail by Harrington and Ganshorn.[8]

The origin of leiomyosarcomas has not been established. No conclusive evidence has been offered in support or denial of either the theory advanced by Cohnheim,[18] that leiomyosarcomas arise from embryonal cell rests, or that proposed by Obendorfer[19] that they represent malignant change in benign leiomyomas.

These tumors have been found to occur with equal frequency from the third through the seventh decades of life. Nine of the fifteen reported cases were women.

Leiomyosarcomas were found most commonly in the third portion of the duodenum, but because of the small number of cases this point is not considered significant. In 6 cases, the tumor arose primarily in the third portion; in 4, in the second portion; and in 3, in the first portion. In 2 cases, both the second and third portions were involved, the site of origin not being determinable.

Growth is usually away from the intestinal lumen, but extreme friability and ulceration of the mucosa overlying the tumor, giving rise to bleeding, is not uncommon. Necrosis within the tumor, followed by suppuration and the formation of fistulas, considered characteristic of these tumors, is due to their poor vascular supply. Extension, when it occurs, is usually by direct contiguity. Metastasis to other organs is uncommon, having been reported in 4 of the 15 cases. In each instance, metastatic deposits were noted only in the liver.

The symptoms associated with tumors of the duodenum are in no way diagnostic. Those cited in this series of cases in order of frequency were: (1) weakness and fatigue, (2) loss of weight, (3) dyspepsia, (4) melena, and (5) upper abdominal pain. Jaundice related to obstruction of the common duct is uncommon, in spite of the intimate relationship of several of these tumors to the ampulla of Vater and terminal portion of the common duct. This undoubtedly can be attributed to the infrequency of invasion of surrounding structures.

Because of the low-grade invasive quality of these tumors and because growth is usually away from the intestinal lumen, they characteristically have attained large size by the time they become manifest clinically. Of the 13 cases in which the size was recorded, 6 were 8 cm. or more in greatest diameter, 3 were 5 cm. to 8 cm. and 4 were less than 5 cm. In 9 of the 15 cases, a palpable upper abdominal mass was evident.

Roentgenographic study has proved one of the most valuable adjuncts in the diagnosis of lesions of the gastrointestinal tract. The limitations of these studies must be recognized, however, as indicated in this review. Roentgenographic study of the upper gastrointestinal tract was carried out in 12 of the 15 cases. In 4 cases, the radiologist was able to demonstrate changes consistent with a diagnosis of duodenal tumor. In one case, the findings were interpreted as representing carcinoma of the head of the pancreas, and in one, the roentgenogram of the upper gastrointestinal tract showed no abnormality, but that of the colon was suggestive of an extrinsic lesion compressing the transverse colon. Thus, in one-half of the cases, roentgenographic studies were of no diagnostic value. The difficulty the radiologist may encounter is further brought out by the case presented here in which four roentgenographic examinations of the upper gastrointestinal tract failed to reveal the lesion in the second portion of the duodenum. Thus, in spite of careful radiologic evaluation, the primary pathologic lesion may not be found. This should not deter one from careful and repeated examinations even though concomitant abnormalities exist which partially but not wholly offer explanation for the patient's symptoms.

Exploratory laparotomy was required to establish the correct diagnosis in the majority of reported cases. In 7 of these, the diagnosis was proved at operation, in 4, it was made roentgenographically, and in the remaining 4, it was established at post-mortem examination.

Surgical extirpation is the only curative treatment of leiomyosarcoma of the duodenum. In pedunculated subserous growths or small noninvasive lesions, local resection of the tumor with or without removal of the involved segment of duodenum is usually sufficient. However, an invasive lesion or one intimately related to the ampulla of Vater or infiltrating the head of the pancreas may require pancreaticoduodenectomy in one or two stages to effect complete eradication.

In this series of 15 patients, the tumor was resected in 10. Five of the latter survived the immediate postoperative period. Incidentally, the oldest patient of this group (the case reported here) is now asymptomatic and has resumed normal activity nine months postoperatively. This adds further support to the view that operation should not be denied a patient because of advanced age alone when accurate diagnosis and cure of the existing pathologic condition are the objectives.

SUMMARY

A case of leiomyosarcoma of the duodenum in an 80-year-old woman, which was successfully removed, is reported. Sixteen case reports of patients with duodenal leiomyosarcomas have previously appeared in the literature; five of these patients survived resection. A review of the case records indicates the difficulty of establishing the diagnosis of tumor in this location.

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MULTIPLE SLIPPED FEMORAL EPIPHYSES

Case Report

Richard H. Eppright, M.D., and Bedford F. Boylston, M.D., Houston, Texas

(From the Department of Surgery, Baylor University College of Medicine and the Orthopedic Service of the Jefferson Davis Hospital)

THERE has been considerable speculation for years as to the cause of epiphyseal separation of the capital femoral epiphysis in adolescence. We have all looked for difficulty in other epiphyses in these cases, but so far there have been no recorded cases in the English literature of multiple slipped femoral epiphyses.

The case presented below is interesting in that the slipped lower femoral epiphysis occurred at the age of twelve years with possibly adequate trauma to explain an acute slip. Though the roentgenograms (Figs. 1 and 2) did not demonstrate the triangular metaphyseal fragment so commonly seen with this injury, particularly of the lower femur, one must assume that this was probably a traumatic slip. Whether there was an underlying epiphyseal defect in this case one can only speculate.

CASE REPORT

J. L., a fourteen-year-old Negro boy, height 5 ft. 3 in., weight 105 pounds, was first admitted to the Jefferson Davis Hospital on Dec. 22, 1947, with a history of having ridden his bicycle into a slow-moving automobile while delivering newspapers. He had immediate pain in the region of the left knee. X-ray examination revealed a complete separation of the left distal femoral epiphysis with displacement of the epiphysis anteriorly. Under general anesthesia a closed reduction was carried out and the patient was immobilized in a one and one-half hip spica with the knee in 30 degrees flexion. The patient regained full motion of the left knee at the end of about three months.

The second admission was on Jan. 28, 1951. While flying a kite and running backward, he struck a rock with his foot and fell to the ground. He had immediate pain in the right hip and was unable to move his right leg. X-ray examination of the pelvis (Fig. 3) revealed a complete displacement of the right capital femoral epiphysis with a minimal slip of the left capital femoral epiphysis. On questioning the patient, it was found that he had one year prior to this admission been told by his schoolteacher that he had a limp and that it should be investigated. Because of only occasional discomfort in the hip, nothing was done.

On physical examination the patient was found to be of average size for his age of fourteen years, his bone age and chronological age being fourteen years. Hair distribution was normal. The right lower extremity was held in marked external rotation and any attempt at movement caused severe pain.

It was quite apparent that this patient had a gradual slipping of the right capital femoral epiphysis, and with minor trauma the epiphysis had become completely separated from the metaphysis. As is noted in the roentgenograms, there was considerable building up of bone on the inferior aspect of the neck. The patient was taken to the operating room, and under spinal anesthesia the right hip was examined and the diagnosis confirmed. A very gentle manipulation and closed reduction were carried out, and check films revealed good reduction to have been obtained. The hip was nailed in situ using a Smith-Petersen

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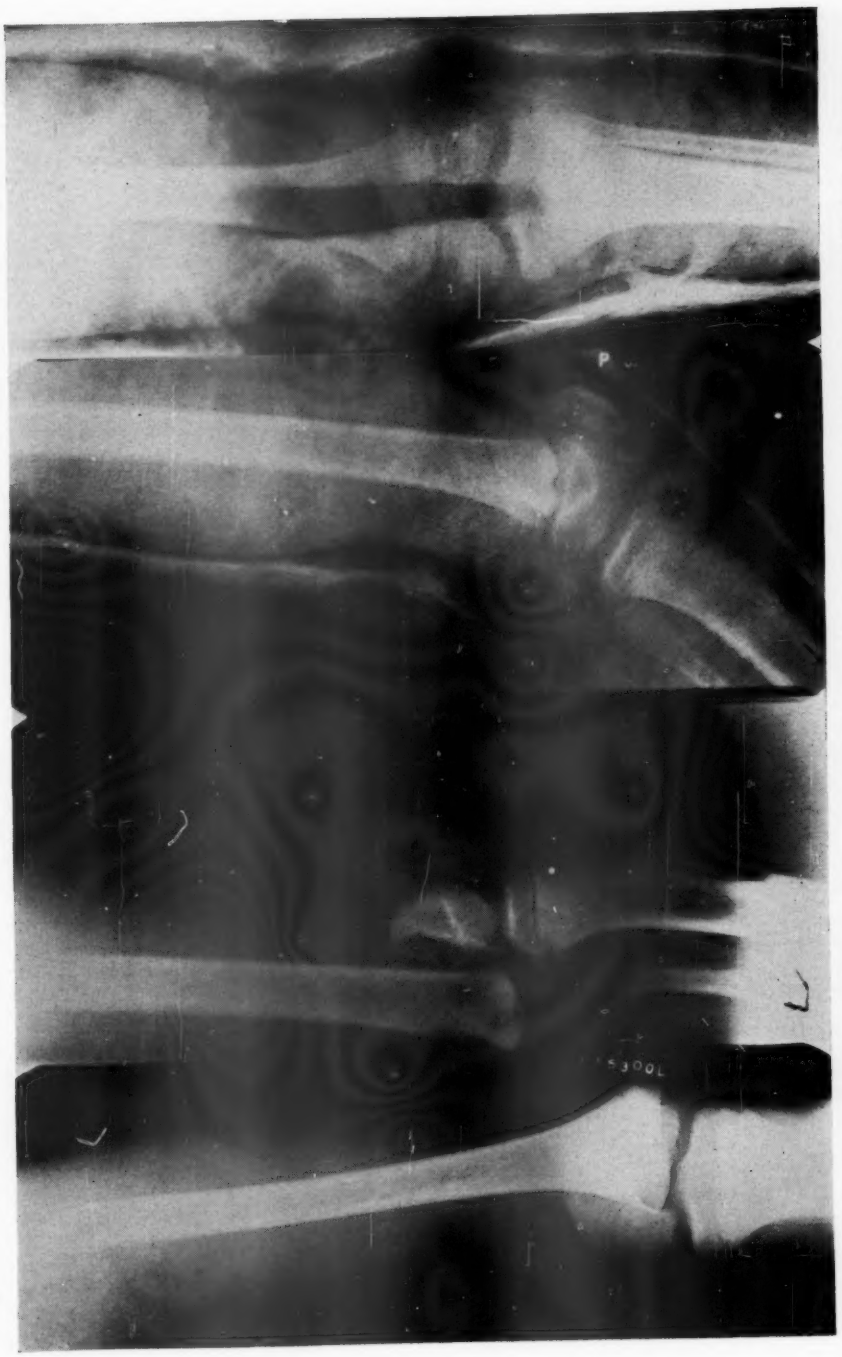

Fig. 1.—Lower femoral epiphyseal slip, December, 1947. Note appearance of triangular metaphyseal fragment.

Fig. 2.—July, 1951. Note line of injury now in femoral shaft. The epiphysis has remained open.

Fig. 3.—Anteroposterior roentgenogram of both hips, January, 1951, with complete separation of right upper epiphysis and minimal separation of left upper epiphysis. Lateral view, minimal slip on left.

nail. Ten days later the left hip was nailed in situ. Postoperatively the patient was maintained in Russell traction for a period of three weeks from the time of the first nailing, and then allowed to be ambulatory on crutches using a four point gait. Crutches were continued for four months.

Laboratory Data.—The calcium phosphorus and phosphatase were within normal limits. The Kolmer and Kline tests were negative.

Fig. 4.—Seven months after nailing, these roentgenograms demonstrate good position of the epiphysis on the right. There is no evidence of aseptic necrosis. Both epiphyseal lines are closing.

On examination on Aug. 25, 1951, the patient walked without a limp. There was no permanent flexion contracture of either hip. Further flexion was possible to 125 degrees on the right, 135 degrees on the left. Internal rotation was 30 degrees on the right,

30 degrees on the left. External rotation was 60 degrees on the right, 60 degrees on the left. Abduction was 45 degrees on the right, 60 degrees on the left. Adduction was 30 degrees on the right, 30 degrees on the left. The leg length as measured from the anterior superior spine to the medial malleolus was 34½ inches bilateral.

SUMMARY

A case is recorded of a fourteen-year-old Negro boy who suffered complete displacement of both the upper femoral epiphysis on the right and the lower femoral epiphysis on the left within a period of two years. There was also minimal displacement (less than 2 cm.) of the left capital femoral epiphysis. No discrepancy in leg length occurred. Seven months after the displacement of the upper femoral epiphyses, the patient walked without a limp, and there was no evidence of aseptic necrosis (Fig. 4).

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

FRACTURES OF THE MANDIBLE

A SERIES OF 434 CASES

MILTON T. EDGERTON, M.D., BALTIMORE, MD., AND
ELMORE HILL, D.M.D.,* BIRMINGHAM, ALA.

(From the Departments of Plastic Surgery and Dentistry of The Johns Hopkins Hospital and University)

THERE have been many recent innovations in the treatment of fractures of the mandible. New methods of fixation have appeared, new and more effective antibiotics have been introduced, and more direct surgical techniques have been utilized. As a result the need for evaluation of these methods of treatment has encouraged the collection and study of the material in this paper. At The Johns Hopkins Hospital, in the last four years, 434 fractures of the mandible have been seen and studied. The patients were treated by one or both of the authors. Primarily because of our own uncertainty as to the best method of treatment of some of these fractures, a wide variety of techniques has been employed. Some of these have proved most useful; others have been helpful only in very special circumstances. In reviewing these cases we have attempted to set up guiding principles to aid us in the future in the choice of treatment of mandibular fractures.

Some general trends have become apparent in comparing this series of fractures with older reports. Among these are the decreased incidence of infection as a complication of fracture and the increased use of both open reduction and fixation with Kirschner wire. With each passing year the higher standard in the evaluation of end results has been accompanied by a decrease in both the number of infections seen and fibrous unions obtained, by a disappearance of the practice of intraoral or "through and through" drainage of fracture lines, and by an improvement in the occlusion obtained on healing of the fracture.

METHODS OF STUDY

All of the 434 cases were freely used to study results and complications, but 100 consecutive cases were carefully analyzed as a statistical guide. Practically all cases were ward patients, and the majority showed extremely unfavorable dental hygiene and therefore a poor prognosis in regard to treatment of their fracture. A large percentage of these fractures were not seen until several days after they had occurred. Many had become infected before the patients came to the hospital.

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We have selected a method of classification of fractures, as suggested by Kazanjian,[8] in which the presence or absence of teeth in the fragments of the mandible is the determining consideration. In single fractures, if adequate teeth remain in both fragments the fracture is designated as a Class 1 fracture. If teeth remain in only one of the two fragments, it is a Class 2 fracture, and if both fragments lack useful dentition it becomes a Class 3 fracture. In multiple fractures where three or more major fragments are present, the fracture is classified as a Class 2 fracture if one fragment is edentulous or as a Class 3 fracture if two or more fragments are edentulous. The classification is further subdivided by indicating the location of the fracture line in all single fractures. As a result of this type of division all fractures in any one bracket would, in general, be treated with the same method of fixation; decision as to treatment thus is greatly facilitated.

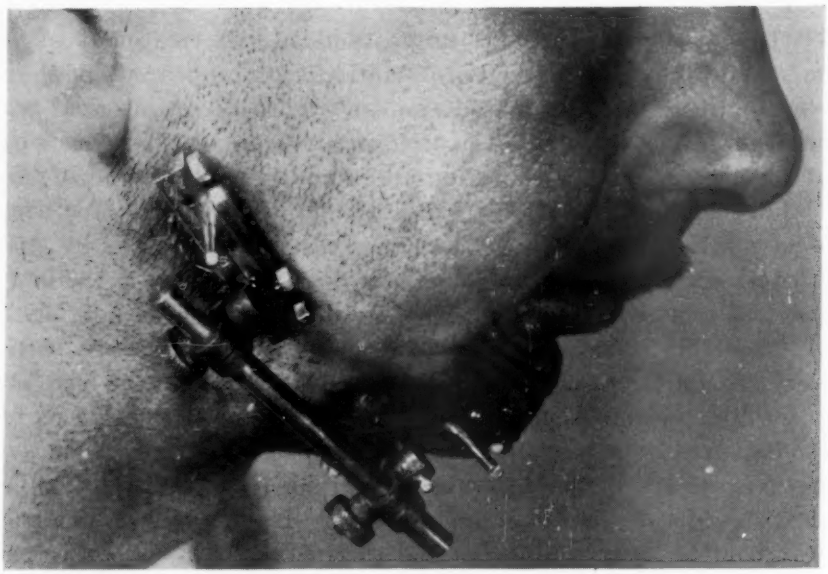


Fig. 1.—Modified Haynes apparatus for fracture of molar region. A universal joint connects each end of the central bar to each two-pin unit. When the fracture line is grossly contaminated and dentition is inadequate for arch bar fixation, this method is preferred to open reduction.

Table I shows the percentages of fractures in each of these classifications. It will be noted that in a very large majority of the fractures at least one fragment was edentulous, and a consideration of some treatment other than intermaxillary wiring was therefore in order. Treatment was based along the following general lines: Stout wiring or intermaxillary wiring with the aid of arch bars was employed in all cases where dentition was adequate, particularly in Class 1 fractures, and in undisplaced Class 2 fractures of the angle, ramus, or condyle. Intraoral splints were utilized in a number of cases but were found troublesome to construct, and they often failed to give adequate fixation. Open reduction was used with increasing frequency and gave rise to surprisingly few complications. In such cases, reduction was almost hairline. External skeletal fixation by the modified Haynes appartus (Fig. 1) was utilized in cases where

we feared infection by open reduction, but the complications were numerous, though rarely serious. Loosening of the pins, salivary fistulas, and occasional distraction of the fracture line were all seen. Circumferential wiring proved to be both tedious and likely to provide imperfect fixation. Table II shows the percentage of fractures treated by the various methods, and Table III lists the complications encountered.

TABLE I. ANATOMIC CLASSIFICATION OF 320 MANDIBULAR FRACTURES*

LOCATION OF FRACTURE LINE	CLASS 1 (PER CENT)	CLASS 2 (PER CENT)	CLASS 3 (PER CENT)
Symphysis	3	½	1
Mental foramen	10	1	1
Molar region	3	4	0
Angle	5	26	1
Ramus		2	0
Condyle		5	1
Coronoid		½	0
Multiple fractures	8	22	6

*Of these, 78 per cent were compound fractures, and 3 per cent represented massive loss of bone such as is encountered in gunshot wounds.

TABLE II. TREATMENT USED IN 100 CONSECUTIVE MANDIBULAR FRACTURES

METHOD	PER CENT
Intermaxillary wiring	
a. Stout wiring	23.4
b. Arch bars with elastics	42.3
Open reduction	
a. External incision	13.5
b. Intraoral wiring	0.9
Intraoral dental splint plus arch bars	6.3
External skeletal fixation (Haynes apparatus, etc.)	4.5
Circumferential wiring	0.9
Liquid diet and Barton bandage	3.6
Kirschner wire fixation	4.6

TABLE III. COMPLICATIONS ENCOUNTERED IN MANDIBULAR FRACTURES

COMPLICATION	PER CENT
A. Infection	
1) Abscess formation (62 per cent of these were present on first examination)	8.1
2) Osteomyelitis	1.8
B. Non-union or fibrous union (40 per cent of these were a result of gunshot wounds with massive loss of bone)	4.5
C. Malunion	1.0
D. Salivary fistula	0.6

It may be seen that approximately 66 per cent of all fractures were handled adequately by means of Stout wiring or arch bars with elastic traction. The remaining 33 per cent offered the more interesting cases for study as regards the choice of treatment.

The conclusions, based on the end results obtained, seem more easily expressed by considering the various anatomic sites of the fractures.

SITES OF FRACTURE

A. *Symphysis.*—Most of these fractures are Class 1, and it has long been recognized that the strong pull of the mylohyoid and digastric muscles makes immobilization difficult and gives rise to a relatively high percentage of non-unions or fibrous unions. In considering fractures of the symphysis it has not been generally emphasized that retained teeth in *or even very near* the line of fracture are especially likely to give rise to infection of the fracture site. Such infection certainly accounts for some of the fibrous unions obtained in the past. There is also a distressing tendency of the lower dental arch to lose its normal width, especially if bone and teeth have been lost. This condition is best prevented by the use of a simple crib splint as described by Ivy and Curtis.[7] Elastic traction applied to the crib over a period of several days may be needed to restore occlusion.

With these anterior fractures of the symphysis we now extract all teeth that are in the line of fracture or that have been loosened even slightly. In most such cases the blood supply to these teeth has been disrupted. Posteroanterior radiographs should be supplemented with periapical films in order that the exact position of the teeth in relation to the fracture line may be observed. If adequate teeth remain, arch bars and elastic traction are used to reduce the fracture over a period of several days. The type of bar used by us* can be adapted to the arch continuously rather than in sections. The fracture is first reduced manually if there has been displacement, and the fracture site is then spanned by this rigid arch bar. Excellent stabilization of the fragments may usually be obtained. A crib is added if there is a tendency of the arch to collapse transversely.

In Class 1 fractures the remaining teeth on either side of the fracture line are often either insufficient in number or so located that adequate stabilization cannot be obtained by an arch bar alone. In such cases, particularly if elastic traction fails to reduce the fracture, some less conservative method of fixation is called for. We have found the introduction of two crossed Kirschner wires to be simple and effective (Brown and McDowell[4]) (Fig. 2, *A*, *B*, *C*). Anteriorly the mandible is thick and the wires are easily inserted with little danger to vital structures. The fracture is reduced manually with the aid of local anesthesia at the time of insertion of the wire. The use of either the Haynes apparatus or of open reduction, on the contrary, may fail to maintain adequate fixation in the presence of strong torque forces acting in the mental region. While it is realized that enthusiasts for external skeletal fixation are able to show excellent results with the Haynes or other types of pin fixation on fractures of the symphysis, we have obtained our best results, with fewer complications, by using fixation with Kirschner wire. Although these wires often cross the fracture line of compound fractures we have seen no instance of osteomyelitis. Penicillin therapy is routinely administered for seventy-two hours.

We have also found it wise to immobilize these fractures 10 to 14 days longer than other single fractures of the mandible. This increased period is based on the possibly reduced blood supply of a midline structure and the strong tendency of the mylohyoid muscles to "rock open" these fractures.

*Designed by Dr. John Erich.

B. *Mental Foramen.*—This group of fractures is important because of its frequency. Most of these fractures are Class 1 and as such may be treated with Stout wiring or arch bars and the use of intermaxillary elastics. It might be

A.

B.

C.

Fig. 2.—*A*, Severe comminuted fracture of symphysis and right mental foramen region. An assistant reduces the fracture manually while an electric drill is used to insert the Kirschner wires.

B, Only one end of each wire is left exposed for later removal.

C, Ends of wires have been covered by cork. Patient also suffered a laceration of parotid duct and facial nerve. Wires were left in for five weeks.

stated that Stout wiring requires three adjacent teeth for proper use and there is some possibility that this method may damage the peridontal membrane. For these reasons arch bars are generally to be preferred, particularly if there are several missing teeth.

In fractures of the mental foramen the short (posterior) fragment is usually elevated and the chin often shows lateral deviation toward the side of the fracture. The fracture line usually parallels the backward and downward slope of the tooth roots, and displacement is greater if the upper jaw lacks opposing teeth.

Our present mode of treatment in this group has been the use of arch bars and the extraction of teeth in the fracture line. We have deliberately left a tooth in the fracture line in five of these patients and carried out "prophylactic" external drainage. All of these fractures healed without complication. The patients were of course given penicillin for a short period (7 days). The teeth remained vital in all five. If there is a separated triangular fragment along the lower border of the mandible, open reduction has been used in most cases. Good union without infection was obtained in all of these fractures. Erich and Austin[5] suggest the use of a molar band (orthodontic anchor clamp) when only a single tooth remains in the posterior fragment, but even in these cases we have found that an arch bar is sufficient.

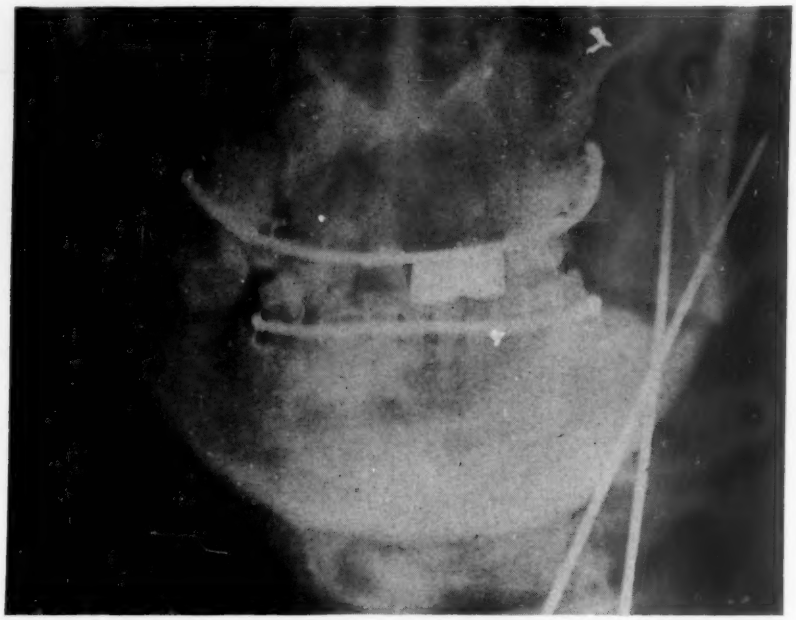
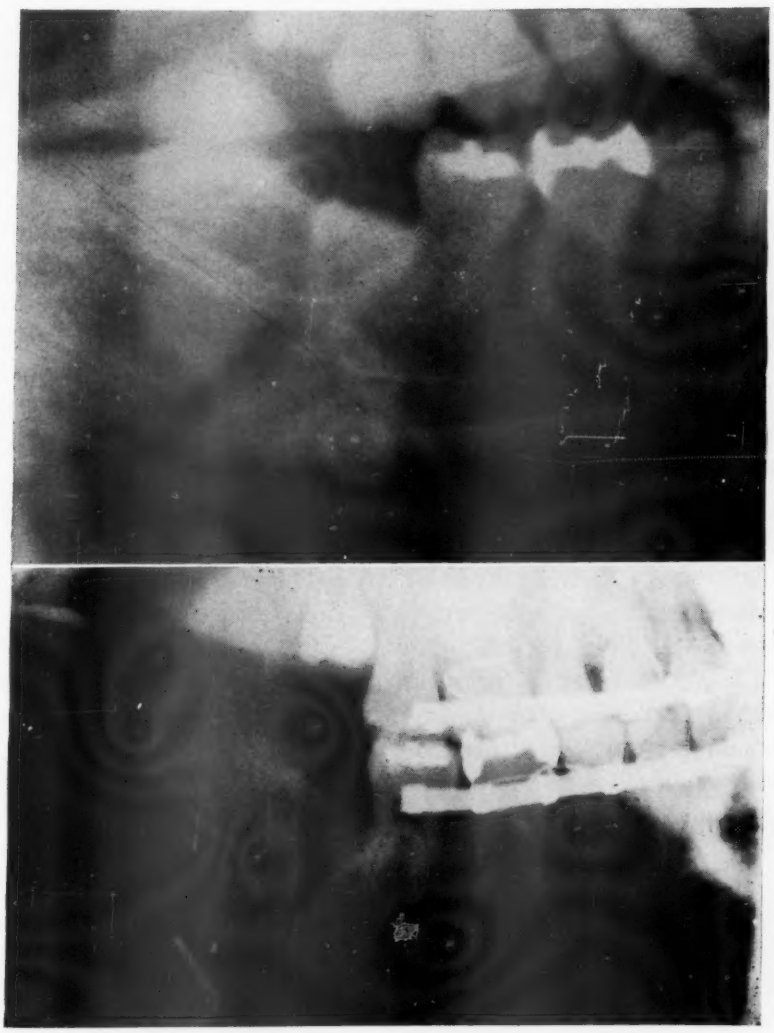


Fig. 3.—Film showing Kirschner wires inserted for angle fracture. The wires are somewhat difficult to insert with fractures in posterior mandible. A single wire is sometimes sufficient.

In Class 2 fractures of the mental foramen, with a long edentulous posterior fragment, we have combined the use of an arch bar with an extension acrylic saddle splint that fits over the edentulous fragment and holds it down. This procedure has given routinely good results, and we have seen no pressure necrosis of the mucous membrane. With Class 3 fractures of the mental foramen we initially employed circumferential wiring, but in the last two years we have come to rely on open reduction for this group. The circumferential wiring was much more difficult to carry out, and we have encountered no additional complications with open reduction.

C. *Molar Region.*—This group of fractures may in general be handled in a very similar manner to those in the region of the mental foramen. Arch bars, of course, are preferred with Class 1 fractures, open reduction or external skeletal fixation being used with Class 3 fractures. We have found that the use of

A.



B.

Fig. 4.—*A,* Fracture at angle through impacted third molar with minimal superior displacement of posterior fragment. Impacted third molar should be removed from line of fracture. Open reduction is method of choice since this is a fresh fracture and tooth removal will often allow posterior fragment to pull up unless it is held.

B, Film showing fragments in good position following removal of impaction and open reduction. Obliquity of wiring prevents any late upward shift of posterior fragment.

Kirschner wires applied directly across the fracture line is less satisfactory with posterior fractures than with the anterior group (Fig. 3). This is due to the thinness of the ramus and the more difficult angle of approach to the posterior fractures. Occasionally writers suggest the use of elaborate interdental splints

rather than intermaxillary elastic traction. It should be pointed out that these splints require additional patient visits in order to take impressions and additional time to prepare the splint.

Splints are often inadequate for proper reduction and fixation of fractures of this group. One good example is a fracture of the molar region with medial and superior displacement of the posterior fragment. While a saddle-type dental splint will usually depress the posterior fragment to the proper level, it often fails to correct the medial displacement. If splints of the onlay type are used, the final occlusion may be modified if proper relief has not been given to the occlusal contact points. In addition, such splints are expensive, are not conducive to good oral hygiene, and are not well tolerated by the patients.

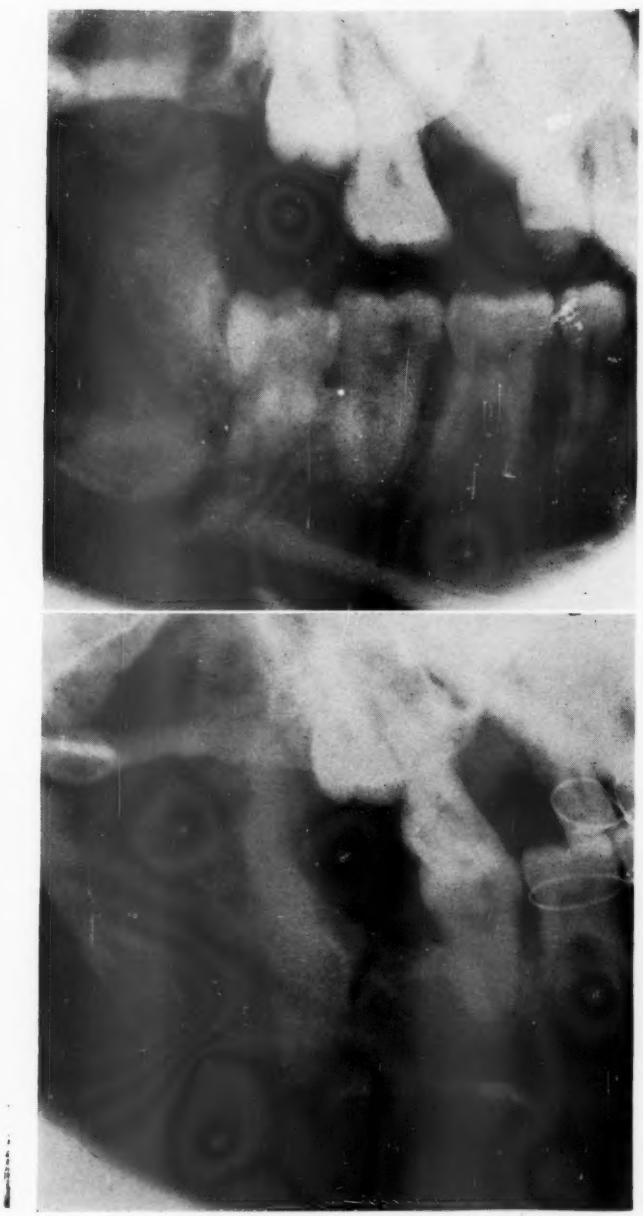
D. *Angle.*—This group of fractures made up 32 per cent of all single fractures and the majority of the multiple fractures contained one angle fracture. Perhaps in this type of fracture more than in any other we found it most worth while to individualize the treatment. Fractures of the angle may be posterior to all teeth, or the fracture line may involve the most posterior molar on that side. In addition the fracture line may be grossly displaced or may show almost no displacement, and the fracture may be either fresh or several days old when first seen. It is the combination of these conditions which will determine the treatment in each instance.

In the case of fresh fractures, posterior to all teeth, in which there is no appreciable displacement, Stout wiring with intermaxillary elastics provided adequate fixation. This was true even if the fracture line ran from above downward and backward (that is to say, was "unfavorable"). The same treatment can be used if the fracture line involves only the crown of the last remaining molar. If, however, there is significant displacement, open reduction is carried out through a tiny cervical incision, and the bone is reduced by means of a single steel wire applied obliquely across the fracture line (Fig. 4, *A* and *B*). The incision is closed without drainage. Fresh angle fractures which involve at least one root of a molar tooth and in which there is no displacement of the fracture line, are treated by removal of the tooth if this can be carried out without displacing the fracture line. If there is periapical disease present or even questionable pulp involvement, the tooth is always removed and a drain is inserted through an external incision; otherwise the fracture line is not drained and intermaxillary wiring is added (Fig. 5, *A* and *B*). If the tooth is impacted or if the fracture line lies in an "unfavorable" direction, it is often best to apply intermaxillary elastics, leave the tooth undisturbed to avoid displacement, and drain the fracture line externally through a small incision. The tooth can be removed in three weeks, unless at that time it remains vital on percussion and there are no signs of local infection. We have observed such teeth closely and have found that most of them can be saved (Fig. 6).

Fractures seen within the first 48 hours are classified as "fresh fractures." Such fractures of the angle, involving the last molar tooth in which definite displacement of the fracture line has occurred, are now treated by removal of the tooth and external open reduction with transosseous wiring. These frac-

ture lines are not drained. Occasionally, one is able to carry out manual reduction, and if the fracture line can then be impacted, simply intermaxillary wiring may suffice (Fig. 5, *B*).

A.



B.

Fig. 5.—*A*, Fracture at angle through socket of third molar with superior displacement of posterior fragment. Fracture was 72 hours old and infection would almost surely have developed if tooth had been left in place.

B, Film showing good position of fragments following removal of third molar and manual reduction. If fragments can then be impacted, this may allow operator to avoid open reduction.

Our series of fractures included a large number of angle fractures seen after a lapse of several days. If the fracture line in these cases lies posterior to the last tooth, and no displacement is present, arch bars or Stout wiring are

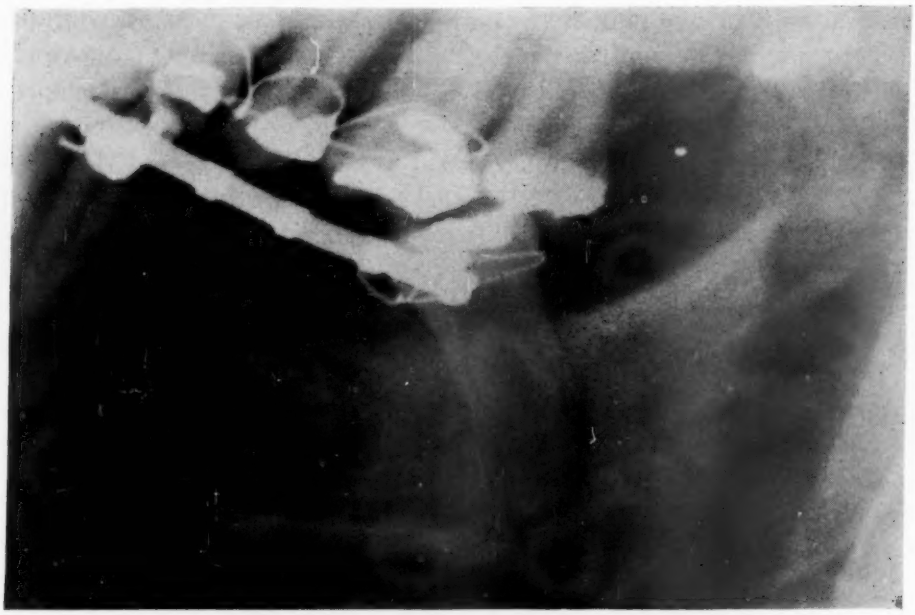


Fig. 6.—Nondisplaced fracture communicating with apex of third molar. Fracture was drained externally and arch bar was applied. The third molar was vital two months later. (Ink used to intensify fracture line.)

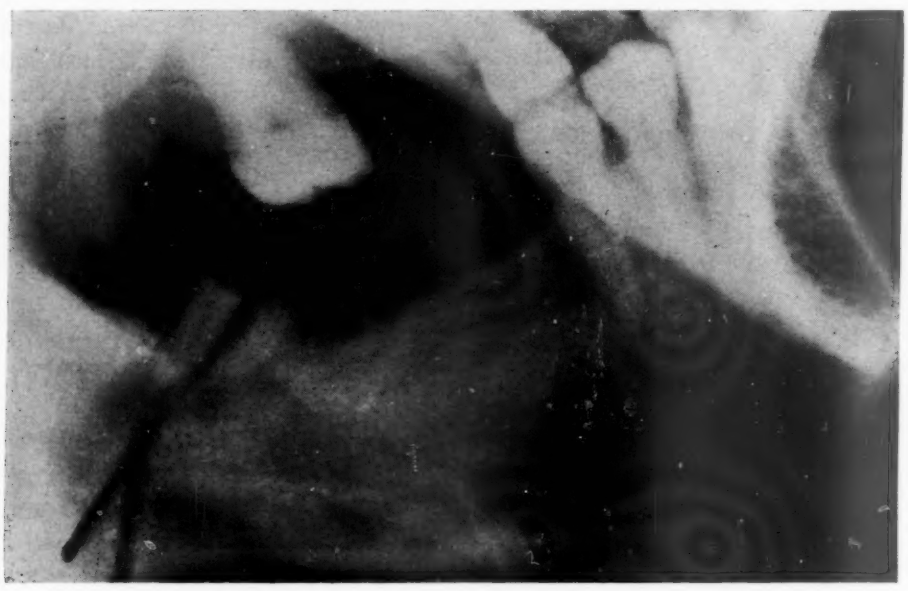
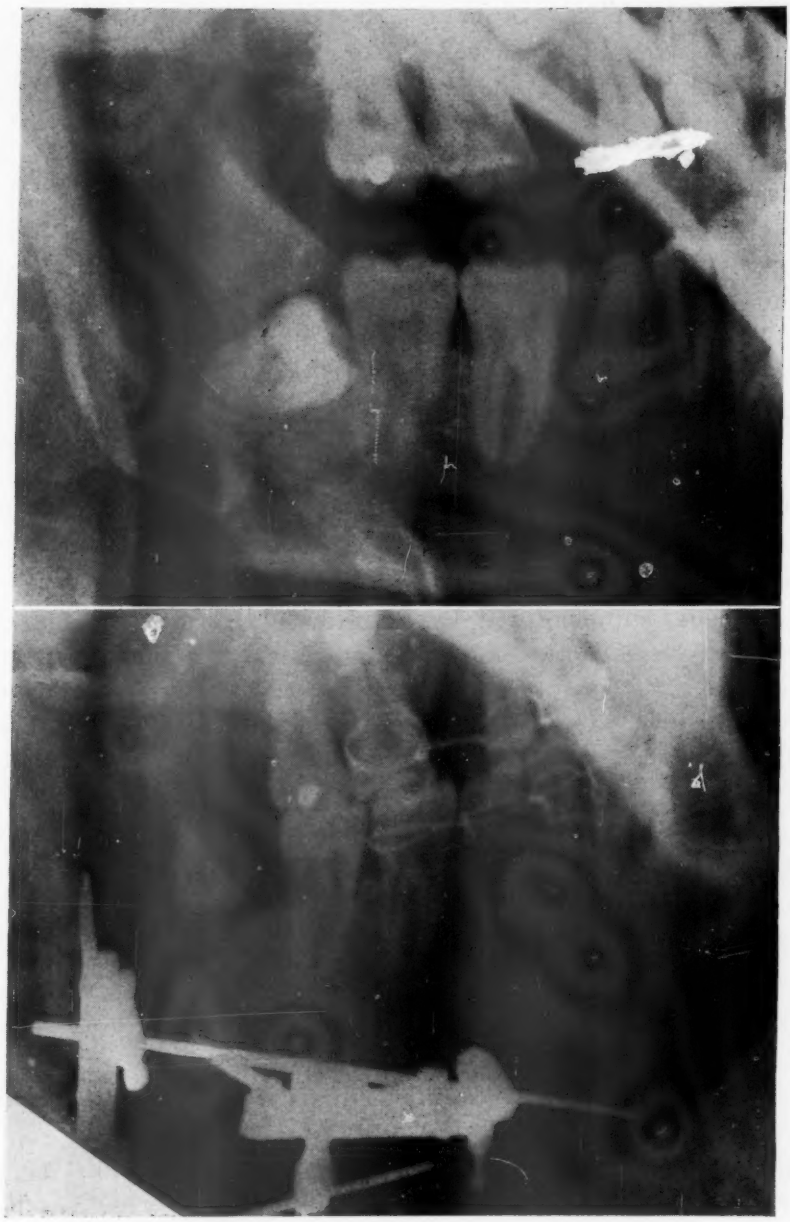


Fig. 7.—Fracture at angle through cariously destroyed third molar. Any teeth with apical pathology should be removed from line of fracture immediately. We have found it wise also to drain this type of fracture line externally.

again utilized. If there has been marked displacement, open reduction is again employed with little hesitancy as such fractures are almost never compounded. With old fractures through the root of a molar tooth, or even with fresh frac-

tures through a carious tooth root (although there is no displacement of the fracture line), we now always remove the tooth and insert an external drain (Fig. 7).

A.



B.

Fig. 8.—*A*, Five-day-old untreated fracture of angle with considerable displacement superiorly and overriding of fragments. Tooth was removed but reduction and impaction of fracture line were impossible.

B, Film showing fragments in good position following the application of a Haynes-Griffin appliance. Open reduction was contraindicated because of time lapse and purulent drainage from fracture site. Drain was placed to fracture line through cervical incision. (Ink used to intensify reduced fracture line.)

A considerable number of fractures were seen in which the fracture line contained a periapically diseased tooth, and a number of these were treated without external drainage but with extraction of the tooth, if the fracture was a fresh one. It is possible that external drainage need not be always instituted in such patients. However, if such a drain is not placed it must be recognized that the chance of infection is many times greater than when such extracted teeth appear healthy, and one should at least urge close observation and a longer period of chemotherapy than usual. Finally, with old angle fractures that pass through a tooth root and that are displaced by the original fracture or by the attempt to remove the tooth in a nondisplaced fracture, we would now routinely make sure that such a tooth is removed, and that external drainage is carried out. The incision for external drainage usually makes it possible to gain a glimpse of the fracture line, and for that reason a Haynes apparatus or other form of external skeletal fixation may be rather easily applied (Fig. 8,*A* and *B*). If reduction is difficult with the Haynes apparatus, we have found that a posterior extension arm can be added to the lower arch bar and dental compound may be applied to this arm in such a manner as to hold down the posterior fragment. It may be noted that, even with the aid of chemotherapy, we have hesitated to use open reduction on a fracture line that has been both exposed to invasion by organisms of the oral cavity and without immobilization for several days.

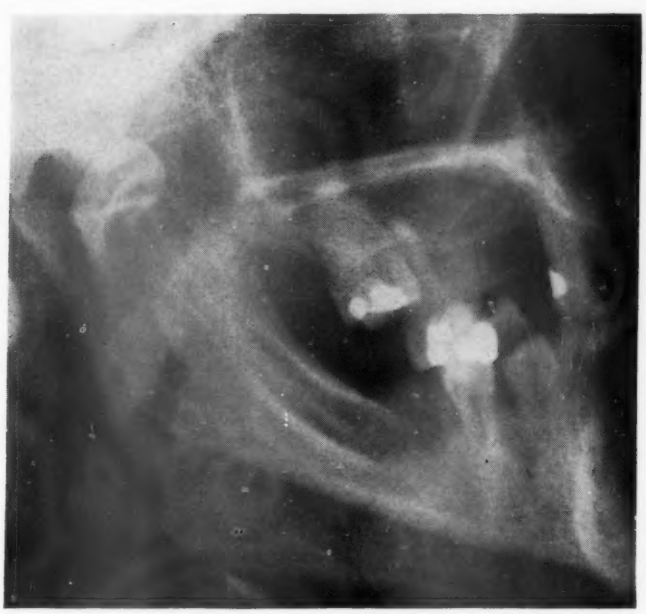
With Class 3 angle fractures (an edentulous mandible) open reduction without drainage, supplemented by an external Barton bandage and liquid diet, offers a very satisfactory method of treatment. Previous papers by many writers have referred to the use of intraoral open reduction with transosseous wiring. In this series we have had occasion to use that procedure a number of times. It would seem clear, however, that there is very little to recommend it for the following reasons:

1. The procedure is accompanied by obviously more contamination of the fracture line than is open reduction through a cervical incision.
2. Access to the fracture line is technically more difficult.
3. Reduction is usually not as exact as with the external exposure.
4. The wire within the mouth is often uncomfortable and requires later removal before "seating" a denture.
5. Because of the continued presence of saliva and mouth organisms with intraoral open reduction, osteitis frequently develops around the wire used for fixation.

Balanced against these objections is the possibly greater danger to the facial nerve with an external open reduction. This danger can be virtually eliminated by using a transverse short (2 cm.) cervical incision just below the fracture line. The incision should be through skin only; the remainder of the soft tissue may then be spread bluntly with a hemostat. We have had no injuries to the facial nerve and no complaints about the almost invisible scar that remains.

E. *Ramus.*—These fractures are not common and are usually easily treated. Most often the fibers of the masseter and pterygoid muscles prevent gross displacement of the fractured fragments, and the bone is deeply placed and the

A.



B.

Fig. 9.—*A,* Posteroanterior view showing bilateral condylar fracture with dislocation of condyle heads medially.

B, Right lateral film showing anterior dislocation of condyle head. Marked trismus and swelling prevents adequate manual reduction.

fracture is seldom compounded. Treatment usually consists of four weeks of intermaxillary wiring. With fractures of the ramus, trismus is the commonest complication in our series, for which two methods of treatment have proved outstandingly useful. Rubber corks used as wedges between the teeth will relieve most cases of trismus and will work much better than elaborate exercisers. Most cases clear within one week after active motion is begun. Five per cent of the patients using corks continued to have some trismus for three to four weeks. The use of deep nerve block of the mandibular nerve where it emerges from the skull will often break up the muscle spasm and decrease pain. The needle should be inserted through the skin of the cheek and the block may have to be repeated two or three times. Two per cent procaine or Xylocaine may be used.

A. *B.*

Fig. 10*A* and *B*.—Same patient shown in Fig. 9 after 6 months of conservative management with elastics and fulcrum splinting. Occlusion is good and there is only slight stiffness in left temporomandibular joint on chewing.

F. *Condyle.*—In nondisplaced condylar fractures, immobilization for a period of three weeks will suffice. In the more complicated condylar fractures in which there is dislocation, there is often a marked open bite due to shortening of the ramus. Intermaxillary traction ordinarily will suffice to return the mandible to normal occlusion, particularly if there is an adequate complement of posterior teeth. In the absence of posterior teeth, a splint may be inserted in the molar region which serves as a fulcrum to provide leverage when traction is applied anteriorly and thus brings the jaws into proper relationship.

The literature is full of conflicting reports as to whether patients with dislocated condylar fractures should be subjected to immediate condylectomy or only to conservative wiring together of the teeth in a position of occlusion.

We believe that these patients should not be subjected to excision of the condyle as an emergency measure or even within the first few weeks after injury. In this early period the tissues are tight with traumatic edema. The patient has had no chance to evaluate the amount of ultimate subjective discomfort or limitation of jaw motion, and he is thus in no position to choose between continuation of those symptoms and the possible complications of surgical treatment. Furthermore, these fractures are often bilateral and the surgeon may frequently avoid operating on one, or even both, sides by allowing a period of several weeks for the symptoms to subside. The results with late operation are just as satisfactory as with immediate operation.

Fig. 11.—Left lateral film showing similar displacement of right condylar head. This case was also treated conservatively by insertion of an acrylic fulcrum splint in the molar area and application of elastic traction anteriorly. Five months later the patient was able to chew quite well without discomfort.

Over 90 per cent of the displaced condylar fractures in our series obtained a satisfactory result by simple intermaxillary wiring and the occasional use of a fulcrum splint between the molar teeth (Figs. 9 and 12). In most of these patients there was measurable, but only slight, limitation in jaw action, particularly affecting the lateral motions of the pterygoid muscles.

G. *Multiple Fractures.*—Thirty-six per cent of our fractures were multiple. Approximately 22 per cent of these were Class 1 and 25 per cent were Class 3. The remainder showed one major fragment with no teeth in it (Class 2). The remaining teeth were used to immobilize as many fragments as possible, and in general, any edentulous fragment was then held by one of the methods described above under single fractures of the same anatomic location.

Here again we found no need to employ head caps or elaborate intraoral splints. Apparatus of the Haynes type (Fig. 1) was used less frequently as time passed, and open reduction became more common as it appeared that we were encountering no serious complications. At one poin' we were tempted to try open reduction on a number of compound fractures seen over 72 hours after injury and containing edentulous fragments. Eleven patients were so treated, without drainage of the fracture line. Eight healed promptly and without purulent discharge. Three showed collections of purulent material in the soft tissue. Incision and drainage were then carried out down to the steel wire *but without removal of the wire.* All three wounds healed promptly, and the wires still remain in place. The use of open reduction and wiring is not to be

Fig. 12.—Patient with bilateral condylar fracture. Acrylic fulcrum may be glimsped in right molar region. Elastics on arch bars serve to bring anterior teeth up into occlusion and at the same time prevent shortening of the vertical height of mandible posteriorly.

recommended routinely for contaminated fracture lines, but the results in these eleven cases suggest that we may have a tendency to be unduly fearful. Of course, antibiotics may be the important new feature.

All of the severely comminuted fractures and those with massive loss of bone from gunshot wounds are found in the group of multiple fractures. For this reason over 90 per cent of the nonunions and fibrous unions in our series are found in this category.

COMPLICATIONS

A. *Infection.*—Table III shows that this complication was seen in 8.1 per cent or in one out of twelve mandibular fractures. Sixty-two per cent of these infections, however, were present when the patient was first seen. They were

obviously a result of no immobilization, retained teeth and tooth roots, and very poor dental hygiene. It is doubtful whether such presenting infections can be reduced in number. The remaining 38 per cent of these infections of soft tissue developed while the patients were under treatment. A breakdown of these cases again showed that some of these infections were probably incipient when the patients were first seen as they became apparent within 72 hours of the first visit. In retrospect, however, it is felt that a few of the infections could probably have been prevented by a slightly different method of treatment. A total of ten patients with infection were considered to be in the potentially preventable group. Three of these were patients in whom carious teeth were extracted from the line of fracture. Because the fractures were fresh, the fracture lines were not drained externally. Although no sequestra formed, cervical abscesses developed in all three, with consequent delay in healing. Since that time a large number of infected teeth have been extracted when they lay in the fracture line, with simultaneous application of an external drain. In none of these has a soft tissue abscess developed. The presence of apical dental disease in the fracture line is thus probably a good indication for external drainage even though the tooth is removed.

Five of the ten "preventable" infections observed were found to have developed in patients who were first seen over 72 hours after injury. The fracture lines involved at least one tooth, which was removed in each case. Although fixation was adequate in these patients no external drain was inserted, and a note was made on the records of four of these patients that a purulent drainage was noted within the mouth at the site of the fracture. More recently we have made it a policy to carry out external prophylactic drainage of any fracture lines first seen over 72 hours after injury if they involve a tooth, even though the tooth is also removed. These drains are usually left in place about six days. The remaining two patients in the group having so-called "preventable" infections, for reasons of their own removed the arch bars and elastics and failed to return for their regular appointments over a period of one to three weeks. Here again we attributed the infection to lack of fixation, which allowed constant motion of the bone fragments, resulting in trauma to the mucosa and permitting saliva to work into the fracture line.

We have not made the diagnosis of osteomyelitis unless sequestra have formed or unless there has been definite radiographic evidence of bone destruction. We have seen this complication in less than one out of fifty mandibular fractures. This is most surprising in view of the unbelievable neglect that many of these patients showed in regard to both treatment and dental hygiene. Our very frequent use of a short course of penicillin undoubtedly accounts for the significant decrease in the occurrence of this complication. Treatment has been conservative with prolonged fixation and removal of sequestra as they are formed. Bone grafting is only rarely required.

B. *Non-union.*—Four and one-half per cent of the fractures showed non-union, or, more commonly, fibrous union. Forty per cent of the patients in this group were first seen with massive loss of bone such as that resulting from a gunshot wound. In this group initial non-union was felt to be unavoidable.

Three patients were seen with pathologic fractures resulting from malignancy, one with multiple myeloma, one with metastasis from carcinoma of the breast, and one with metastasis from thyroid carcinoma. Two of these fractures failed to heal. The remaining cases of non-union were all present in patients in whom infection of the fracture line was noted, suggesting that if infection can be avoided and adequate fixation provided, union is likely to occur.

C. *Malunion.*—This complication resulted in one patient with a previous fracture on the contralateral side of the mandible that had been allowed to heal without the placing of the teeth in occlusion. It would have been necessary to refracture this old fracture to give this man proper occlusion. Because of his age and blindness this was deemed inadvisable. An additional case of malunion of a condylar fracture was seen with symptoms of continuing pain in the region of that joint. This was corrected by condylectomy.

D. *Salivary Fistula.*—This complication was seen only in connection with external skeletal fixation. In two patients troublesome discharge of parotid secretion developed at the site of insertion of the pin. On removal of the pin one of these fistulas closed within 48 hours; the other continued to drain for two weeks, and then closed spontaneously.

SUMMARY

A study of 434 mandibular fractures is presented. A comparison of various therapeutic methods is undertaken, and an analysis of the complications encountered is made. The discussion is largely confined to present-day controversial points in the management of these fractures. Improved results would seem to be related to the use of antibiotics, better methods of fixation, and careful application of the principles of surgical drainage, particularly in the case of the more difficult fractures. In this clinic, with increasing experience, open reduction and Kirschner wire fixation have become more satisfactory, and accordingly circumferential wiring, head caps, and elaborate dental splints are used less often.

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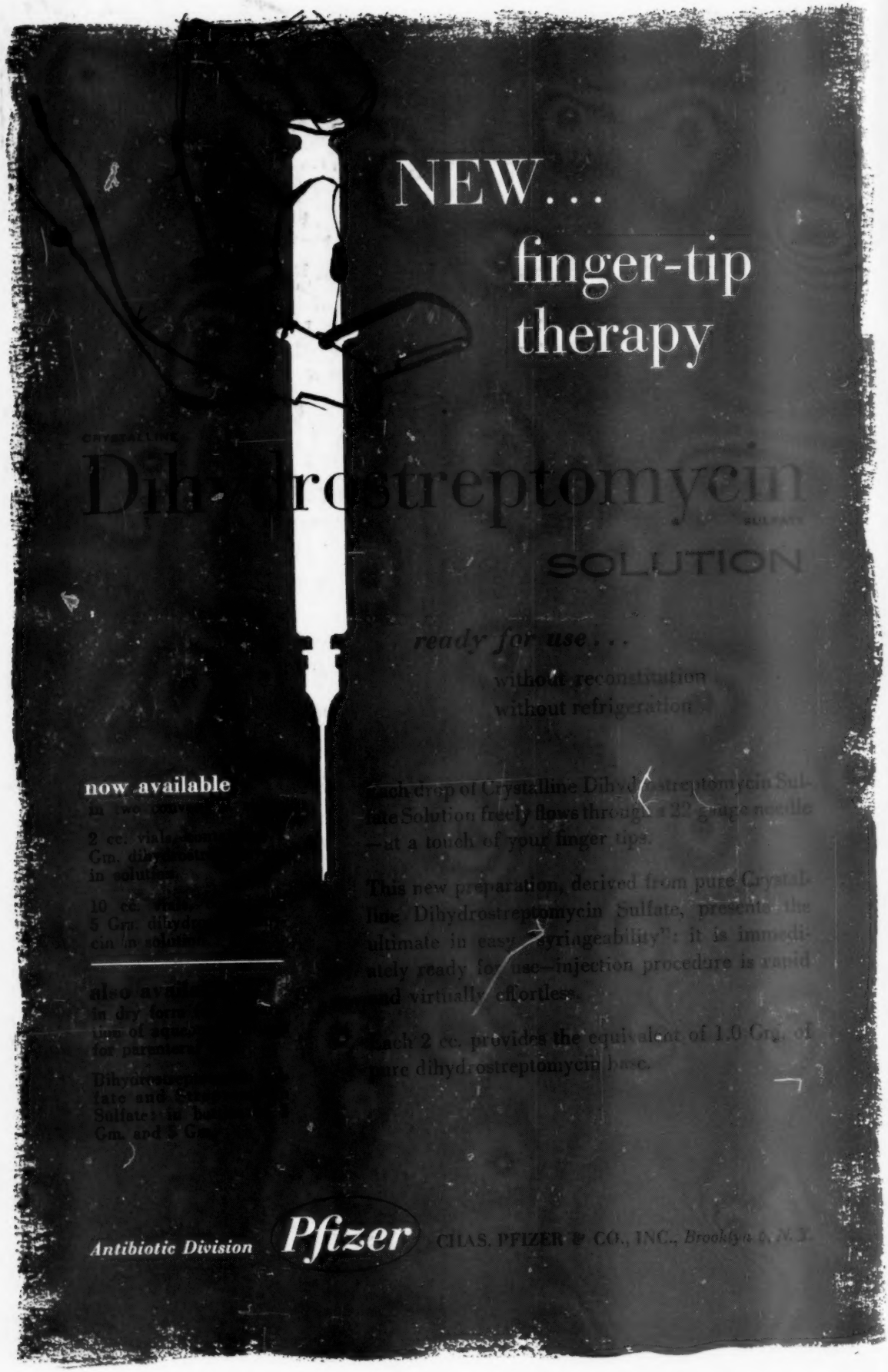
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